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Vol. 223 No. 1 JANUARY, 1952 No. 957

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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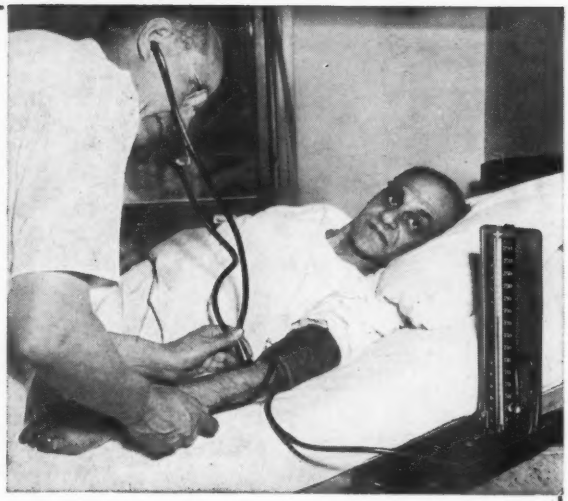

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1952

ORIGINAL ARTICLES

THE SHORT-TERM EFFECT OF PITRESSIN IN RHEUMATOID ARTHRITIS

By George G. Haydu, M.D.
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AND
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It was suggested in 1948 by one of us (G.G.H.) that the rheumatoid process in rheumatoid arthritis patients is based on an enhanced tissue activity, particularly for adenosintriphosphate (ATP), and an attendant defection of the rapid energy donating system[12]. The evidence offered was derived from the differential response of rheumatoid arthritis patients where ATP was regenerated through the use of insulin and glucose, or insulin and sodium lactate[15]. The follow-up of the same patients produced additional data which were amenable to the same interpretation[16]. All the data were obtained through the study of glucose utilization in rheumatoid arthritis patients and control groups under identical conditions on the Second Division, Goldwater Memorial Hospital.

In 1949 Binkley[2] reported that pitressin produces a very characteristic inhibition of adenosintriphosphatase activity. This effect seemed to be a suitable tool for the further study of the pathogenesis of rheumatoid arthritis. For, if the increased adenosintriphosphatase activity of the tissues is basic to the nature of rheumatoid arthritis, the inhibition of it should bring an alleviation of many of its symptoms. Preliminary studies showed that this was the case, and that 4 units of pitressin were sufficient to achieve it. Pitressin was employed only for the study of the pathogenesis of rheumatoid arthritis and not as a form of therapy.

Pitressin must be administered with great caution. Mills and co-workers[25] reported myocardial infarction after the routine use of pitressin for cholecystography. It was found earlier that pitressin produced general myocardial ischemia[9]. Beyond such cardiac effects, pitressin raises the blood pressure quite uniformly[26]. For these reasons, only such patients were selected in this study whose blood pressure and electrocardiograms were normal.

Procedure and Results. The patients were observed in such a manner that the diagnosis of their joint pains, stiffness, and limitation of joint motion was established after the short-term effect of pitressin had been studied. In this way, objectivity of evaluation was achieved. After the observation of the pitressin effect, the diagnosis was recorded. The data of patients subsequently found to be rheumatoid arthritics appear in Table 1, and the data

of those found to be traumatic or osteoarthritic cases appear in Table 2. Erythrocyte sedimentation rates were determined on all patients (Westergren method[34]) and are indicated in all tables. Throughout this study 4 units of pitressin were given intramuscularly.

Table 1 shows clearly that rheumatoid arthritis patients respond quickly and substantially to pitressin. There is a considerable reduction of pain and stiffness, and a significant increase in the motion of the joints. When saline solution is injected, there appears no such change in pain, stiffness, and motion. Table 2 indicates that patients suffering from pain and stiffness due to trauma or osteoarthritis are not improved and do not have an increase in the range of joint motion after pitressin injections.

Thus pitressin, an inhibitor of adenosintriphosphatase activity, electively improved the pain, stiffness, and motion of rheumatoid arthritis patients. It is also apparent from Table 1 that

TABLE 1.—RESPONSE OF PATIENTS WITH RHEUMATOID ARTHRITIS BEFORE AND AFTER INTRAMUSCULAR ADMINISTRATION OF 4 UNITS OF PITRESSIN

Case and Sed. Rate†	*Subject Observed*	*Before Pitr.*	*After Pitressin (minutes)* 15	30	45	60	*Evaluation of Response*
S. L.	Pain	2+	1+	0	0	0	
	Stiffness	2+	1+	0	0	0	
30/h	Left elbow*	135	150	165	165	165	Good
	Right elbow	135	145	150	155	155	
	Left knee	150	165	170	170	165	
	Right knee	155	165	170	170	165	
M. P.	Pain	2+	2+	0	0	1+	
	Stiffness	2+	1+	0	0	0	
25/h	Left ankle	65	80	85	95	70	Excellent
	Right ankle	80	100	120	90	90	
L. F.	Pain	2+	2+	1+	1+	1+	
	Stiffness	3+	3+	1+	0	2+	
134/h	Left knee	50	55	90	80	80	Excellent
	Right knee	45	55	65	65	65	
	Left ankle	30	45	40	50	30	
	Right ankle	35	60	70	70	60	
S. G.	Pain	3+	1+	0	1+	1+	
	Stiffness	3+	1+	0	1+	1+	
44/h	Left wrist	80	120	135	135	135	Excellent
	Right wrist	50	90	100	90	80	
	Left knee	90	130	135	125	95	
C. G.	Pain	1+	1+	±	1+	1+	
	Stiffness	1+	1+	±	1+	1+	
68/h	Left elbow	90	90	95	90	90	Negligible
	Left ankle	75	75	85	75	75	
H. R.	Pain	1+	0	0	0	0	
	Stiffness	1+	±	0	0	0	Excellent
22/h	Left ankle	50	80	85	85	85	
R. Z.	Pain	1+	1+	±	±	±	
	Stiffness	2+	2+	1+	1+	1+	
142/h	Left wrist	20	20	35	45	45	
	Right wrist	35	35	45	45	55	Moderate
	Left shoulder	30	45	55	55	55	
	Right shoulder	35	50	50	50	65	
C. S.	Pain	3+	2+	1+	1+	1+	
	Stiffness	3+	1+	0	2+	2+	Excellent
91/h	Left ankle	70	80	105	105	90	

† Westergren method * Numbers after joints indicate degrees of motion

the greatest response of rheumatoid patients was reached generally in 30 minutes.

We have known since 1949 that the adrenocorticotropic hormone of the anterior pituitary gland effects a dramatic remission in rheumatoid arthritis[17]. This remission of ACTH is produced through the adrenal cortex. The possibility that pitressin acts through the adrenal cortex, or that some admixture of ACTH occurs with pitressin had to be considered, although the ACTH effect takes longer than the short-term effect of pitressin described above.

When the adrenocortical function increases, there follows a considerable and sensitive reduction in the number of the circulating eosinophils[33]. This reduction of eosinophils reaches its maximum in 4 hours[19]. We examined additional rheumatoid arthritis patients after the administration of 4 units of pitressin. In addition to the behavior of pain, stiffness, and joint motion, the number of circulating eosinophils was observed. The determination was done according to the modified Dunger method[7]. The counting was performed before the pitressin ad-

TABLE 2.—RESPONSE OF CONTROL PATIENTS BEFORE AND AFTER INTRAMUSCULAR ADMINISTRATION OF 4 UNITS OF PITRESSIN

Case and Sed. Rate†	*Diagnosis*	*Subject Observed*	*Before Pitr.*	*After Pitressin (minutes)* 15	30	45	60	*Evaluation of Response*
S. H.	Sprain	Pain	3+	3+	3+	3+	3+	
		Stiffness	3+	3+	3+	3+	3+	None
4/h		Right ankle*	20	20	20	20	20	
E. M.	Osteo-	Pain	0	0	0	0	0	
	arthritis	Stiffness	1+	1+	1+	1+	1+	None
16/h		Left wrist	110	110	110	110	110	
J. R.	Trauma	Pain	2+	2+	2+	2+	2+	
		Stiffness	2+	2+	2+	2+	2+	None
5/h		Right shoulder	70	70	70	70	70	
G. Q.	Sprain	Pain	2+	2+	2+	2+	2+	
		Stiffness	3+	3+	3+	3+	3+	None
27/h		Left elbow	120	115	115	115	115	
A. S.	Osteo-	Pain	1+	1+	1+	1+	1+	
	arthritis	Stiffness	1+	1+	1+	1+	1+	None
18/h		Right wrist	85	85	85	90	90	
J. B.	Trauma	Pain	2+	2+	2+	2+	2+	
		Stiffness	2+	2+	2+	2+	2+	None
4/h		Right knee	80	80	80	80	80	
E. W.	Osteo-	Pain	2+	2+	2+	2+	2+	
	arthritis	Stiffness	2+	2+	2+	2+	2+	None
9/h		Lumbar spine	20	20	20	20	20	
M. N.	Trauma	Pain	2+	2+	2+	2+	2+	
		Stiffness	1+	1+	1+	1+	1+	None
5/h		Right shoulder	80	80	80	80	80	

† Westergren method

* Numbers after joints indicate degrees of motion

ministration and ½ hour and 4 hours after the administration.

The results appear in Table 3. They indicate that the improvement as to pain, stiffness, and joint motion is quite general. The eosinophil count shows a significant increase. A general increase of leukocytes was also noted, but it is not included in this study. The marked increase in the number of the circulating eosinophils is quite uniform. Thus one can exclude the possibility

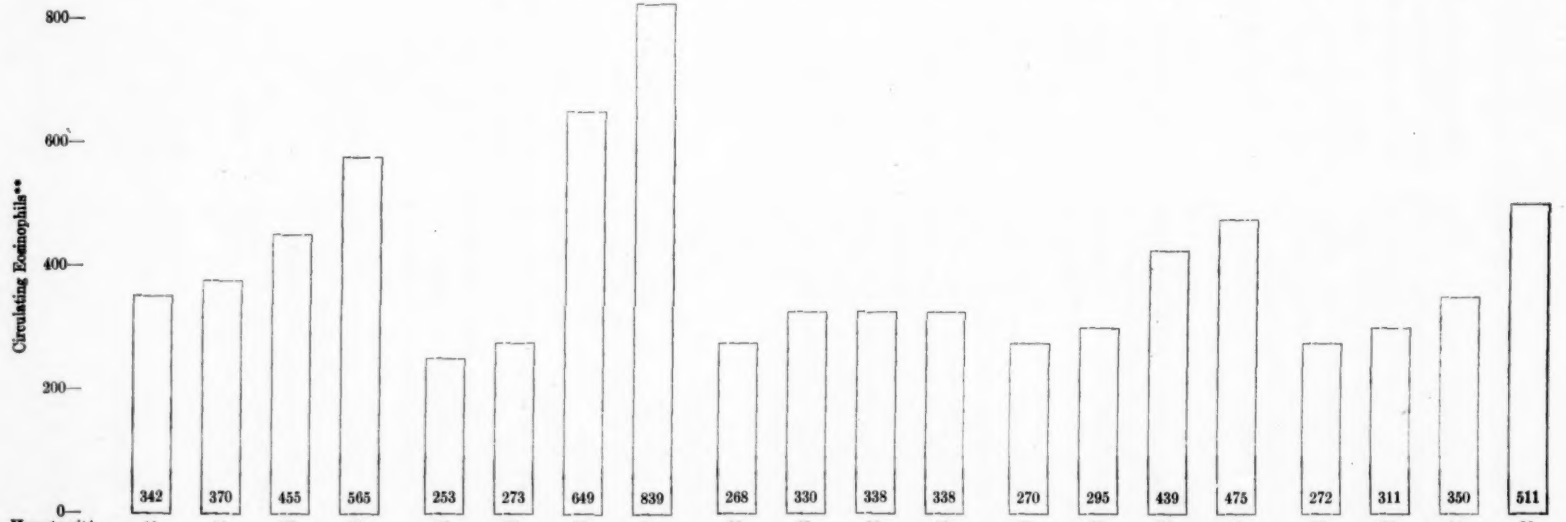
TABLE 3.—EFFECT OF 4 UNITS OF PITRESSIN ON THE NUMBER OF CIRCULATING EOSINOPHILS, AND ON PAIN, STIFFNESS AND JOINT MOTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

	Case: G. G. Sed. rate:† 82/hr. Joint observed: left knee				Case: A. B. Sed. rate: 58/hr. Joint observed: right elbow				Case: J. O. Sed. rate: 68/hr. Joint observed: right knee				Case: B. L. Sed. rate: 130/hr. Joint observed: left metacarpal				Case: M. L. Sed. rate: 72/hr. Joint observed: left ankle			
	Pitressin				Pitressin				Pitressin				Pitressin				Pitressin			
	Bef.	After			Bef.	After			Bef.	After			Bef.	After			Bef.	After		
		½ hr.	4 hr.			½ hr.	4 hr.			½ hr.	4 hr.			½ hr.	4 hr.			½ hr.	4 hr.	
Pain	2+	1+	1+		2+	1+	1+		1+	0	±		1+	1+	1+		1+	0	±	
Stiffness	1+	0	0		2+	1+	1+		1+	±	1+		2+	0	1+		1+	0	±	
Joint motion*	15	30	15		50	75	90		90	105	110		30	80	70		35	90	45	
Circulating Eosinophils‡	203	253	420		94	142	256		337	597	709		236	427	569		63	152	220	

† Westergren method
* In degrees
‡ Dunger method

TABLE 4.—EFFECT OF 4 UNITS OF PITRESSIN ON HEMATROCIT VALUES, ON THE NUMBER OF CIRCULATING EOSINOPHILS AND ON PAIN, STIFFNESS, AND JOINT MOTION IN PATIENTS WITH RHEUMATOID ARTHRITIS DURING 24 HOURS

	Case: C. M. Sed. rate:† 46/hr. Joint observed: left knee				Case: A. S. Sed. rate: 99/hr. Joint observed: left metacarpal				Case: C. M. Sed. rate: 81/hr. Joint observed: right shoulder				Case: L. C. Sed. rate: 72/hr. Joint observed: right elbow				Case: M. N. Sed. rate: 129/hr. Joint observed: left knee			
	Pitressin				Pitressin				Pitressin				Pitressin				Pitressin			
		After				After				After				After				After		
	Bef.	½ hr.	4 hr.	24 hr.	Bef.	½ hr.	4 hr.	24 hr.	Bef.	½ hr.	4 hr.	24 hr.	Bef.	½ hr.	4 hr.	24 hr.	Bef.	½ hr.	4 hr.	24 hr.
Pain	2+	1+	1+	2+	2+	0	0	1+	1+	0	0	0	2+	1+	1+	1+	1+	0	0	0
Stiffness	2+	1+	±	1+	2+	±	±	1+	2+	1+	1+	1+	2+	1+	1+	1+	2+	1+	1+	1+
Joint motion*	50	75	75	75	15	30	40	40	15	25	15	15	35	45	45	45	45	60	45	45
Circulating Eosinophils**	342	370	455	565	253	273	649	839	268	330	338	338	270	295	439	475	272	311	350	511
Hematocrit‡	41	41	39	39	38	38	37	36	38	42	39	42	35	35	34	33	32	34	32	33



† Westergren method
* In degrees
** Dunger method
‡ Wintrobe method

that pitressin transacts its effect in rheumatoid arthritis through the adrenal cortex.

It was reported[4] that pitressin produces hemoconcentration. This effect could possibly mask a reduction in the number of circulating eosinophils. To ascertain such an effect, if any, hematocrit values were determined according to Wintrobe[35] in another group of rheumatoid patients, and the response was followed over 24 hours. In the case of ACTH administration, the decrease of eosinophils carries over to the next day.

Table 4 shows the relevant data. Here again, the pitressin effect is apparent as before, and the reduction in pain, stiffness, and limitation of motion is generally achieved in a half hour. This effect is also observable the next day in an attenuated form. The number of the circulating eosinophils continues to increase, and the 24-hour figure is higher than the preceding figures.

The initial hematocrit values are uniformly below normal. This is in good accord with the hypochromic anemia found in rheumatoid arthritis patients. During the 24-hour period there was no significant change in hematocrit values; no evidence of hemoconcentration was observed.

Discussion. The short-term effect of pitressin is clear-cut. The pain and stiffness of rheumatoid arthritis is quickly ameliorated, while the pain and stiffness caused by trauma or osteoarthritis are not affected. Several types of pain have been distinguished in rheumatoid arthritis[13]. In this respect no differentiation could be made, when the alleviation of symptoms by pitressin was studied. It is not suggested here that pitressin be used for treatment in this manner; its short-term effect was used solely for the study of the pathogenesis of rheumatoid arthritis.

The effect of pitressin as described above is somewhat unexpected when one considers the fact that it produces a constriction of the capillaries[22] and the arterioles[5]. Patients show a marked pallor but do not feel weak or faint, and are quite surprised when such a blanching effect is called to their attention.

Selye[31] has demonstrated that desoxycorticosterone can produce the rheumatoid type of tissue lesions. It is interesting to note that there is a physiological antagonism between pitressin and desoxycorticosterone[29]. Such antagonism is evident also in our present study. Some adrenocortical steroids produce eosinopenia, while pitressin produces eosinophilia.

Pitressin inhibits adenosintriphosphatase activity[2]. Inhibition of adenosintriphosphatase activity is also brought about by gold and copper salts[3,8,27], both of which have proved useful in the treatment of rheumatoid arthritis[10,11]. In addition to gold and copper salts, salicylates have specific effects in rheumatic diseases. Lutwak-Mann[23] has found that salicylates selectively inhibit dehydrogenase activity. One may recall that dehydrogenase and adenosintriphosphatase activities are closely related. Not only are both of them inhibited by inactivation of the sulfhydryl groups[1], but in muscle, actomyosin has both adenosintriphosphatase and dehydrogenase activities under the very same circumstances[32]. Thus it seems that inhibition of certain enzyme activities of the tissues has a good therapeutic effect in rheumatoid arthritis. The beneficent effect of such inhibitions confirms findings which suggest that in rheumatoid arthritis one deals with heightened enzymatic avidity of the tissues[15,16]. It has been indicated[20,28], on the basis of clinical experience, that there is a prodromal stage to rheumatoid arthritis. In the patient's history we could usually find a period

of exhaustion which precedes any pain or joint involvement. And before the period of exhaustion there is a period of high effort. Sometimes this high effort is an infectious disease, but most often, it is a prolonged mental or physical stress of the patient's daily existence[12]. Once factors influencing rheumatoid arthritis are considered from such a point of view[14], our data will be consistent with clinical experience.

Effort is transacted mainly through the adrenal cortex. The studies of Selye[30] make these events clearer. The high effort of tissues is stimulated or sustained by the hormones of the adrenal cortex during the alarm reaction. These hormones increase the alkaline phosphatase content of the tissues significantly[21], especially during the alarm reaction[18]. One may note at this point that the optimal adenosintriphosphatase activity of the tissues lies at pH 9[6,24]. It seems, then, that the dramatic effect of cortisone[17] is brought about by the reestablishment of the pre-arthritic stage of high effort. Large doses of cortisone may even increase the high effort level of the tissues, and discontinuation of it may bring an aggravation of the disease.

The effort level of the tissues cannot be looked upon as a mere increase of one substance or another. Much rather is it connected with the functioning status of lipid membranes[36]. Among other functions ATP donates the quick energy needed for the maintenance of the membranes' proper functioning condition[37-40]. The requirement for ATP, the ability and necessity of tissues to utilize and dephosphorylate ATP, is the tissues' adenosinetriphosphatase activity. One can gain very little insight into such activity by making extracts of minced muscles and examining the extract's ability to dephosphorylate ATP[41]. Hill pointed this out in his recent review[42]. Previously Dubuisson[43] in his painstaking electrophoretic studies showed that such factors as fatigue lower the solubility of muscle proteins. He also could demonstrate[44] that when muscles are fatigued by stimulation (and their condition is thus somewhat similar to the state of tissues of the rheumatoid patient), extracts of such muscles contain only beta myosin and no actomyosin. The very same method of extraction will thus gain different fractions of the muscle protein according to the physiological or pathological status of the patient; such fractions do not admit comparison.

The tissue's effort level cannot be brought down to the physiological through adrenocortical hormones. These substances will buttress the high effort level and prevent in this way, for a time, the histochemical derangements of rheumatoid arthritis. A search for elective methods of reducing the tissues' high effort levels may result in the definitive therapy of rheumatoid arthritis.

Summary. 1. Pitressin, an adenosintriphosphatase inhibitor, reduces the pain, stiffness, and limitation of motion of patients with rheumatoid arthritis.

2. Pitressin does not reduce pain, stiffness, and limitation of motion due to trauma and osteoarthritis.

3. The short-term effect of pitressin begins in half an hour, and continues into the next day to a lesser degree.

4. This pitressin effect is not transacted through the hyperfunction of the adrenal cortex; circulating eosinophils are not decreased.

5. After pitressin administration there develops a marked eosinophilia which continues into the next day.

6. No hemoconcentration was observed after the injection of pitressin.

7. The short-term pitressin effect confirms previous studies which indicate that the heightened adenosintriphosphatase activity of tissues underlies the rheumatoid process.

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THE TREATMENT OF LUPUS ERYTHEMATOSUS DISSEMINATUS WITH CORTISONE*†

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After Hench and his associates[7] had demonstrated the effectiveness of cortisone in the alleviation of symptoms in rheumatoid arthritis, it seemed logical to test this therapy in another disease of the collagen group. Therefore, when 17-hydroxy-11-dehydro-corticosterone (cortisone) became available to us for clinical trial it was decided to test its efficacy in lupus erythematosus disseminatus (L.E.D.), since this ordinarily fatal condition was not readily amenable to any other type of therapy, and it was hoped that its progress might be stayed or arrested. Thus we commenced treatment of the first patient November 20, 1949. Since then 9 patients have been treated.

Some published reports are now available indicating that both adrenocorticotropic hormone (ACTH) and cortisone are capable of exerting beneficial effects in this disease. Thorn and his associates[11] reported that 3 patients experienced marked clinical improvement during the administration of ACTH in daily doses of varying size. Elkinton *et al.*[3] similarly obtained improvement in 2 patients, temporary in 1, a remission of 60 days after cessation of therapy in the the other. Grace and Combes[5] noted striking temporary improvement with fading of the skin lesions in 2 classical cases of disseminated lupus erythematosus treated with ACTH.

Boland[1] observed beneficial effects in disseminated lupus erythematosus and in dermatomyositis. Schwartz and Sonne[9] reported benefit in 2 patients and questionable results in another. Soffer, Levitt, and Baehr[10] have reported the largest series, 34 patients with the acute disease, treated with either cortisone or ACTH. They found that the clinical manifestations of fever, toxicity, and joint pains promptly regressed more quickly with ACTH, and that the L.E. cells of Hargraves, the urinary signs, leukopenia, thrombocytopenia, and pathologic alterations seen at postmortem examination were not eliminated. Exacerbations following cessation of therapy were prone to occur. They concluded that prolonged and permanent therapy may be necessary. Undesirable effects of therapy were common and included hypertension, edema, mental disturbances, hirsutism, pigmentation, alkalosis, convul-

* The cortisone for the early investigations was allocated by the Committee on Investigation of Cortisone of the National Academy of Sciences, Dr. Chester S. Keefer, Chairman.

† Funds for the purchase of cortisone for this investigation were supplied by the Division of Research Grants and Fellowships, National Institutes of Health, U. S. Public Health Service of the Federal Security Agency.

sions, congestive heart failure, electrocardiographic change, and diabetes mellitus. Thorn *et al.*[12] in a report in 1950 found that the L.E. cells did disappear, after treatment, in 6 patients.

Brunsting, Slocumb, and Didcoct[2] concluded from their experience in treating 7 women with acute lupus erythematosus with either cortisone or ACTH that these hormones exerted a pronounced effect on the symptoms and promoted remissions in some cases. The benefits were temporary, and there was no improvement in the characteristic laboratory phenomena or the tissue reactions of the disease. These observers also noted complications from therapy such as behavior disturbances and psychotic episodes which were reversible. They urged that caution be exercised when these hormones are administered, and that strict laboratory control is indicated. These authors expressed the belief that the greatest benefit from this therapy might be in the management of early cases without irreversible systemic damage. Irons *et al.*[8] found that patients with L.E.D. improved more quickly with ACTH than with cortisone, but because of the high incidence of complications with long-term ACTH therapy they preferred cortisone for control of achieved improvement.

It is not necessary here to elaborate upon the well known symptomatology of lupus erythematosus disseminatus except to state that in all our cases the dermatologic manifestations, arthritis, febrile course, anemia, leukopenia, and renal involvement were evident in varying degrees. The L.E. cells of Hargraves[6] were demonstrated in the sternal marrow of 7 of the 9 patients of this group. There were some additional individual manifestations which will be described in the summaries to be recorded.

Methods. Nine patients, all women, with acute or subacute lupus erythematosus disseminatus were treated. Studies made included complete blood counts, sedimentation rates (Wintrobe tube), urinalyses, serum proteins (burette method), sodium, potassium (flame photometer), non-protein nitrogen, and sugar determinations (electrophoretic colorimeter). Electrocardiograms, chest roentgenograms, measurements of 17-ketosteroids and 11-oxysteroids, and sternal aspirations for L. E. cells were done. Weight records, weekly or oftener, were kept and most of the laboratory studies were repeated, usually at weekly intervals. Bone marrow aspirations were done at the end of a course of therapy and sometimes repeatedly while the patient was under observation.

Four patients were treated with continuous therapy, usually 100 to 200 mg. a day until 6.0 gm. had been given, and 4 patients received 200 mg. daily for 10 days, with repetition of therapy after 20-day intervals for 2 subsequent courses, so that a total of approximately 6.0 gm. was given to each. In 1 patient therapy had to be discontinued after 2.0 gm. had been given.

Case Reports. CASE 1. L.S., a 14-year old girl, entered the hospital on November 22, 1948, with the history that since March, 1947, she had had easy fatigability, a skin eruption of the face, painful joints, orthopnea, dysuria, and frequently fever from 101° F. to 104° F. The hemoglobin at this time was 10.95 gm., erythrocyte count 3,760,000, and leukocyte count 5,300. L.E. cells were found in the bone marrow and erythrocytes in the urine. The electrocardiographic findings suggested subacute pericarditis. With para-aminobenzoic acid (PABA) therapy, 2.0 gm. every 4 hours, there was a remission for 2 weeks.

When the patient was readmitted on January 19, 1949, she complained of fever, nausea, emesis, oliguria, epistaxis, pain in the left side of the chest and abdomen, loss of hair, and spread of the skin eruption to the mouth, feet, and fingers. Physical examination revealed rales bilaterally, pleural effusion at the left base, a friction rub in the left axilla, skin lesions, and painful, swollen joints. A double murmur was heard in the second left and right interspace radiating down the left side of the sternum toward the apex. Chloramphenicol, 17.0 gm., over a 10-day period, caused some regression in the skin eruption and the fever dropped for a few days, and then rose again. She was discharged to continue PABA therapy.

Due to a relapse she was hospitalized elsewhere and received 48,000,000 units of penicillin in 6 days, quinine, and transfusions. Her treatment up until November 19, 1949, when she was readmitted to our hospital for

cortisone therapy, consisted of transfusions and penicillin. The patient was then given 100 mg. of cortisone twice daily for 30 days for a total of 6.0 gm. Twenty-four hours after the drug was started the temperature, which had been rising daily to 103° F., dropped to a maximum of 101° F. for 3 days and then it fell to normal. On the second day of treatment the skin lesions faded, the pain and swelling of the hands and wrists subsided, and the dyspnea and chest pain disappeared. Toward the end of her hospitalization abdominal striae were seen and there was a 30-pound gain in weight due to edema and ascites. Laboratory studies revealed a persistent albuminuria, a low urinary specific gravity, hyaline and granular casts as well as red and white blood cells in the urine. The hemoglobin varied between 9.4 gm. and 10.5 gm. and the erythrocyte count between 2,900,000 and 3,190,000. The leukocyte count varied from 4,900 to 12,225 and the sedimentation rate remained rapid during her hospital residence. The albumin–globulin ratio always showed a reversal, usually varying from 2.0:3.3 to 1.0:2.8. L.E. cells were repeatedly found in the bone marrow. Cessation of cortisone therapy resulted in prompt diuresis. During treatment the urinary excretion of 17-ketosteroids increased from 2.1 to 6.3 mg. and the 11-oxysteroids from 0.255 to 2.48 mg. per 24-hour period.

On re-examination of the patient January 23, 1950, the patient's weight was back to normal. The skin eruption had recurred and puffiness and edema of the face almost occluded the eyes. There were gross cardiac enlargement and pleural effusion. The albumin–globulin ratio was 2.2:1.7 and many L.E. cells were still present in the bone marrow. The patient's rash was worse than it had been before. She expired at home about 3 months later.

COMMENT. This patient with systemic lupus erythematosus disseminatus, complicated by cardiac involvement, showed symptomatic improvement with cortisone. The albuminuria, anemia, L.E. cells in the bone marrow, and reversal of the albumin–globulin ratio persisted in spite of therapy.

CASE 2. J.M.H., An 18-year old girl, was admitted to the hospital on August 8, 1948, for evaluation of recurrent painful joints and occasional fever which had been present since the winter of 1946. The pain in any joint would last for 1 to 5 days. At times urticarial lesions were present on the forehead and tips of the fingers. Sunshine caused aggravation of the symptoms.

Physical examination revealed striae of the legs, a blowing systolic aortic murmur, and a blowing systolic apical murmur. The right hand was swollen, warm, and tender. The hemoglobin was 12.0 gm., erythrocyte count 3,967,000, and the leukocyte count 5,625. The bone marrow contained many L.E. cells. She was discharged to take 2.0 gm. of PABA every 4 hours.

When follow-up observations revealed improvement in the patient's health, the PABA was cut to 2.0 gm. every 6 hours. On October 14, 1948, the hemoglobin was 8.2 gm., erythrocyte count 2,960,000, and the leukocyte count 3,200. With therapy consisting of ferrous sulfate, vitamins, and a reduced dose of PABA (2.0 gm. every 8 hours) there was improvement in the blood picture. In December she developed serofibrinous pleurisy at the right base for which she was hospitalized a few days.

During 1949 the patient continued to take the PABA without any side effects and she felt well, attending college, taking a reduced schedule. L.E. cells persisted in the bone marrow.

On March 22, 1950, she was readmitted with a complaint of a sharp pain in the chest which was found to be due to pleuritis and pericarditis. Fever of 101° was present. On April 10, 1950, she was given 50 mg. of cortisone intramuscularly 4 times a day for 10 days, then 50 mg. twice daily for 40 days. After the first week of treatment, the electrocardiogram showed changes indicating improvement in the pericarditis. By the second week the patient stated that she felt very well and that her appetite was great. The roentgenogram of the chest showed disappearance of the fluid in the left pleural cavity and a return of the heart to normal size. Roundness of the face and hirsutism of the upper lip were seen during the third week of treatment. Even though she was receiving cortisone, swelling and pain of the middle finger of the right hand occurred towards the end of treatment. Just prior to her discharge from the hospital, L.E. cells were still present in the bone marrow and the blood picture was essentially normal. The sedimentation rate throughout her hospital stay was elevated and on discharge it was 44 mm. During treatment the urinary excretion of 11-oxysteroids increased from 0.717 mg. to 2.248 mg. in a 24-hour period while the 17-ketosteroid excretion was not significantly altered.

The patient's last examination, which was in May, 1951, revealed continued subjective

and objective improvement. The hemoglobin was 12.0 gm., erythrocyte count 3,736,000, and the leukocyte count 6,488. A few L.E. cells were present in the bone marrow. She is continuing college work with a reduced schedule.

COMMENT. This patient with joint symptoms, urticarial lesions, and L.E. cells in the bone marrow was given PABA for over a year with good results. Cortisone for 50 days resulted in additional objective and subjective improvement for 8 months and it was extremely useful in the critical period from March to May, 1950, when she was acutely ill.

CASE 3. M.L.K., a farmer's wife, 28 years old, who had a double aortic murmur with a Traube's pistol shot in the femoral arteries along with lupus erythematosus disseminatus, received 50 mg. of cortisone intramuscularly every 6 hours for 10 days. With treatment the excretion of 11-oxysteroids was increased from 0.376 to 1.451 mg. per 24-hour period and the 17-ketosteroid excretion was not significantly changed. There was objective and subjective improvement.

On admission 20 days later for the second course of cortisone therapy which followed the same schedule as the first, the L.E. phenomenon was still present in the bone marrow.This course of therapy produced further improvement in the skin condition and in the patient's general health. Six days after the completion of her third course of cortisone therapy she complained of weakness, palpitation, pain in the chest, dizziness, and bloating. Examination revealed changes suggesting pericardial effusion. Four months later the patient re-entered the hospital because of continued cardiac distress and recurrence of the skin eruption following the extraction of an abscessed tooth. She was given ACTH, 25 mg. in 2000 cc. of 5% glucose by slow drip intravenously daily for 4 days. With this therapy there was a decrease in the heart size as measured roentgenographically, and subjective improvement. On examination 24 days later she stated that she did not tire as easily and that her heart no longer bothered her.

COMMENT. This patient continued to show depression in the hemoglobin and erythrocyte and leukocyte counts; albumin, leukocytes, and erythrocytes in the urine; a low urinary specific gravity; unfavorable changes in the electrocardiogram; increased sedimentation rate; L.E. phenomena; and skin lesions. Her total therapy included 6.0 gm. of cortisone and 100 mg. of ACTH. There was sustained improvement in her condition after each course. Extraction of a tooth appeared to cause a relapse.

CASE 4. M.S., a 34-year old woman whose lupus erythematosus disseminatus was complicated by marked diarrhea and urticaria, was given 100 mg. of cortisone intramuscularly twice daily for 10 days. Within 24 hours after therapy was instituted there was marked improvement. On the sixth day, however, she developed a pneumonitis which subsided with penicillin therapy. On the eighth day of cortisone therapy she developed delirium, with vacillating emotions, loquaciousness, transient visual hallucinations, confusion, agitation, disorientation, and incontinence. At this time a brother stated that the patient had been treated for catatonic schizophrenic episodes on 3 occasions.

COMMENT. Whether or not this patient's mental state was agitated or brought on by cortisone is difficult to state, but it is a probability. This drug did not prevent the development of pneumonitis.

CASE 5. G.C.B., a woman of 47 years of age with systemic lupus erythematosus, had been taking 1.0 gm. of PABA 4 times daily for 5 months with subjective improvement. However, her leukopenia, which varied from 1,000 to 1,300, reversal of the albumin–globin ratio, and the presence of L.E. cells in the bone marrow all remained unchanged.

She received 3 courses of cortisone, 100 mg. intramuscularly twice daily for 10 days with 20-day rest periods between each course. Though the patient noted, with each course of therapy, marked subjective and objective improvement, the laboratory picture continued unchanged as it had with PABA. Follicular pustules of the face, chest and back and hirsutism of the arms developed following cortisone treatment.

COMMENT. As has been frequently observed, symptom control with cortisone is possible, but relapse with cessation of therapy, as in this case, is usual.

CASE 6. A.E.S., a 27-year old woman whose subacute erythematosus started following a streptococcal sore throat and a severe sunburn 5 years before being seen by us, had marked spotty permanent alopecia of the scalp associated with her disease.

This patient received 3 courses of cortisone wherein 100 mg. were given intramuscularly twice daily for 10 days with 20-day rest periods between courses. With the first course she felt jittery, noticed difficulty in hearing, and lost her sense of taste. During the second week after her first course of treatment she stated that she felt the best she had for years and her appetite had been voracious. During the third week, listlessness, loss of appetite and fatigue had been noticed. Following completion of her second course of cortisone the patient remarked that she felt well but the improvement was not so marked as it had been after the first course. No L.E. cells were found in the marrow which was examined before starting the third course of therapy. On the patient's last visit to the clinic 4 months after completion of treatment, there was continued objective and subjective improvement.

COMMENT. This patient's history of frequent sore throats due to a streptococcic infection and of a severe sunburn which occurred at the onset of her lupus erythematosus, re-emphasizes an observation made by many that a focus of infection and a severe sunburn often precipitate the disease. The loss of joint symptoms, decrease in skin lesions, favorable change in her blood picture and electrocardiogram, as well as the disappearance of L.E. cells in the bone marrow would indicate that this patient responded well to cortisone. It is appreciated that failure to demonstrate L.E. cells in a single marrow study does not exclude their presence.

CASE 7. H.C.R., a married woman, 39 years old, whose lupus erythematosus disseminatus was complicated by vasospastic changes of the fingers, had received PABA with improvement, chloramphenicol 7.5 gm. without any change, and surgical sterilization with improvement, before being given cortisone. She received 25 mg. of cortisone 4 times daily for 10 days and then 50 mg. twice daily for 40 days for a total of 6.0 gm. In spite of this treatment the vasospastic symptoms in the fingers continued.

COMMENT. PABA therapy, surgical sterilization, and cortisone therapy in sequence caused temporary objective and subjective improvement.

CASE 8. D.A.W., a 29-year old woman, whose lupus erythematosus disseminatus followed a severe sunburn, had obtained both objective and subjective improvement with quinine, vitamin E administration, and bed rest. Upon a subsequent relapse she was hospitalized for study, and though the signs of the disease were present, repeated examinations never revealed L.E. cells in the bone marrow. The patient received 50 mg. of cortisone intramuscularly 4 times daily for 3 days and then 100 mg. twice daily for 7 days. Then she was given 50 mg. twice daily for 40 days. Within 2 hours after the first injection of cortisone there was an elevation of the temperature which lasted for 5 days. She developed minimal hirsutism, follicular keratosis of the legs, and a moon face. Under therapy there was no significant change in the excretion of the 17-ketosteroids while the 11-oxysteroids excretion increased from 0.579 mg. to 3.257 mg. per 24-hour period.

Three days after her discharge from the hospital there was a recurrence of the skin lesions and this lasted for 2 weeks. Approximately 3 weeks later the patient was given 100 mg. of cortisone twice daily for 5 days because of a relapse. This treatment caused immediate improvement. During the next 6 months of observation the patient suffered from her disease, having exacerbations and incomplete remissions. Testosterone was given to her at another clinic with some improvement.

COMMENT. This patient's flareup of skin lesions and worsening of her health following exposure to the sun is akin to that frequently seen in systemic lupus erythematosus. Although the patient was a classical example of the disease, no L.E. cells were ever found in the bone marrow either at our clinic or elsewhere. The patient's febrile response, when cortisone was started, was similar to the Jarisch-Herxheimer reaction seen in the treatment of syphilis.

CASE 9. S. R. C., a 23-year old housewife, had a 7-year history of transitory, shifting,

swollen, painful, hot and tender joints associated with skin changes characteristic of subacute lupus erythematosus. Gold, PABA, and physiotherapy had given her some relief. The patient received 100 mg. of cortisone twice daily for 10 days. Following a rest period of 20 days she was readmitted for another 10-day course of therapy. She stated that she had not felt so well in the past 5 years as she had following the first course of cortisone. On her third admission 20 days later she remarked as to how well she felt and that her appetite had become excessive. Acneiform pustules had appeared on the forehead and the nasolabial folds. L. E. cells, which were plentiful on her first 2 admissions, were not found on her third admission. During the next 6 months of observation the pains in the joints continued to be present but they were not so severe as they had been before cortisone therapy. Progressive thinning of the scalp hair was the only additional finding.

COMMENT. With treatment this patient improved and with cessation of therapy most of her symptoms recurred, but to a lesser degree. A doubtful-negative test for syphilis represented a biologic false-positive reaction seen in some patients with lupus erythematosus. Acneiform pustules and progressive thinning of the scalp hair developed following cortisone treatment. Symptoms suggesting rheumatoid arthritis often herald lupus erythematosus disseminatus, as they did in this case.

Discussion. Our observations from the treatment of these 9 patients tend to confirm those already reported. It was usual to observe subjective and objective improvement from cortisone therapy but this was not sustained after treatment was stopped. Relapse was the rule and in 1 case, at least, the patient's status was worse 6 weeks after cessation of therapy than before cortisone was administered. In patient J.M.H., however, it appeared that cortisone therapy was very valuable in tiding her over an acute episode with pericarditis and pleuritis, and she has remained as well since cessation of therapy as before cortisone. However, L.E. cells still persisted in the bone marrow in May, 1951. Only 1 patient, M.S., developed serious toxic symptoms in the form of a psychosis which was persistent, although the maintained daily dosage in all cases was considered to be large. This patient obviously was unsuited for cortisone therapy since she had a history of mental disease which was not known until after cortisone therapy had been started.

It seems probable that cortisone and ACTH therapy have value in the control of the acute exacerbations of lupus erythematosus disseminatus, and then it may be life saving. Symptom control is usual with these hormones but certainly no curative value has been established. Incidentally, cortisone therapy has been totally ineffective in 3 cases of dermatomyositis that received similar doses with similar schedules.

It has been our usual experience that therapy with cortisone does result in an increase in the peripheral leukocyte count, but it may not cause complete disappearance of the L.E. cells in the bone marrow. Flood and Limarzi[4] in their studies of the bone marrow before and after ACTH and cortisone therapy found L.E. cells in 15 of 16 patients with acute lupus erythematosus with decrease in the number of L.E. cells after treatment.

It is our impression that the interrupted schedule which we employed is somewhat more satisfactory than the continuous therapy of large doses, 100 to 200 mg. daily for a total of 6.0 gm. Tapering of the dosage and still more prolonged therapy may be wiser still.

Attention to limitation of the salt intake will lessen the likelihood of edema and ascites, and, because of increased potassium excretion, administration of potassium in the form of potassium chloride, for example, 3 gm. a day, might be wise, but in these patients little attention was paid to these de-

tails, although potassium and sodium blood levels were determined repeatedly, usually at weekly intervals.

In treating these patients, one must be alert to the possibility of unfavorable physiologic change of several types, 2 of which we observed, ascites in 1 and a psychosis in another patient. These are but 2 of the many complications that have been described by others.

Five of the 9 patients had received PABA prior to their receiving cortisone. This medicament, which has been shown to be efficacious by Zarafonetis and his co-workers[13] in the treatment of lupus erythematosus, caused subjective and objective improvement which, however, could not be sustained in each instance. Administration of PABA for over a year in Case 2 caused no demonstrable damage. The response to cortisone therapy was more rapid than that with PABA therapy.

Conclusions. 1. From a study of 9 treated cases of lupus erythematosus disseminatus it is concluded that cortisone administration is usually effective in the amelioration of symptoms and signs of the disease, but relapse follows cessation of therapy.

2. Cortisone therapy probably has its chief value in the treatment of acute episodes where it may tide the patient over a critical period and be life saving.

3. Certain complications may arise while cortisone is being administered which may necessitate cessation of therapy or reduction of dosage. These should be watched for so that proper steps for control may be promptly instituted.

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CORTISONE TREATMENT OF TRICHINOSIS*

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The treatment of trichinosis has heretofore been unsatisfactory because of the lack of any therapeutic agent of conclusive value. In view of the known ability of cortisone and pituitary adrenocorticotropic hormone (ACTH) to modify host resistance in a wide variety of other diseases, it was decided to employ one of these preparations in the treatment of a moderately severe case of trichinosis. Cortisone was selected for this clinical experiment and appeared to result in outstanding improvement.

As far as can be determined, there have been no previous reports of trichinosis treated with cortisone or ACTH.

Case Report. History. A 42-year old white male carpenter entered the hospital on March 22, 1951, because of a 2-week febrile illness. He became ill 14 days prior to admission, when he began to experience generalized myalgia, headache, chilly sensations, feverishness, frequent drenching sweats, drowsiness, diarrhea with 4 or 5 liquid stools daily, and cough productive of about 8 ounces of thick yellowish-white sputum in 24 hours. His diarrhea ceased after 3 days, but the other symptoms continued with increasing severity. On about the 4th or 5th day of illness he started to have shaking chills several times a day, occasional nausea and vomiting, sore throat associated with external swelling of the neck, and marked periorbital edema accompanied by conjunctivitis and photophobia. The sore throat, conjunctivitis, and swelling about the eyes and neck were reported to subside 1 or 2 days before admission, while all other symptoms persisted.

One week before the onset of illness the patient had ingested 2 or 3 ounces of uncooked pork sausage. It was subsequently learned that a friend who shared this repast was later hospitalized elsewhere for "pork poisoning".

The patient's past history included a duodenal ulcer since 1943, without any activity in recent years. In addition there was an 8-year history of low back pain, for which no organic cause had been found, and several previous examiners had made a diagnosis of psychoneurosis.

Physical Findings. On admission the patient appeared to be a slender, fairly well-nourished white man of about the stated age who looked acutely ill and held himself stiffly because of diffuse muscular soreness aggravated by movement. The oral temperature was 104.2° F., the blood pressure 100/70, the heart rate 112, and the respiratory rate 24. No periorbital edema was seen, and the conjunctivae appeared normal. The tongue was slightly reddened. There was a cluster of small petechiae in the center of the hard palate. The tonsillar pillars were slightly injected. The heart and lungs were normal. Examination of the abdomen was negative except for a healed appendectomy scar. Generalized muscle tenderness was present, more marked in the lower extremities. There was moderate tenderness to fist percussion over the lumbar spine. The tendon reflexes were hypoactive and equal bilaterally. The neck was supple and no pathological reflexes were noted. The remainder of the physical examination revealed essentially normal findings.

Laboratory Data. The red blood cell count on admission was 5,370,000 and the hemoglobin 16.5 gm. The white cell count was 14,000, with 50% polymorphonuclear leukocytes, 11% "band" forms, 6% monocytes, and 33% eosinophils. Urinalysis was within normal limits except for a trace of albumin in the first specimen examined. A blood Kahn test was negative. Agglutination tests were negative for typhoid, paratyphoid, and Brucella. A heterophile antibody test was positive in 1:28 dilution. The blood urea nitrogen was 19 mg. per 100 cc. Stool examinations were negative for occult blood, and showed no

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

ova or parasites. Blood culture showed no growth. A roentgenogram of the chest was normal except for slightly increased lung markings.

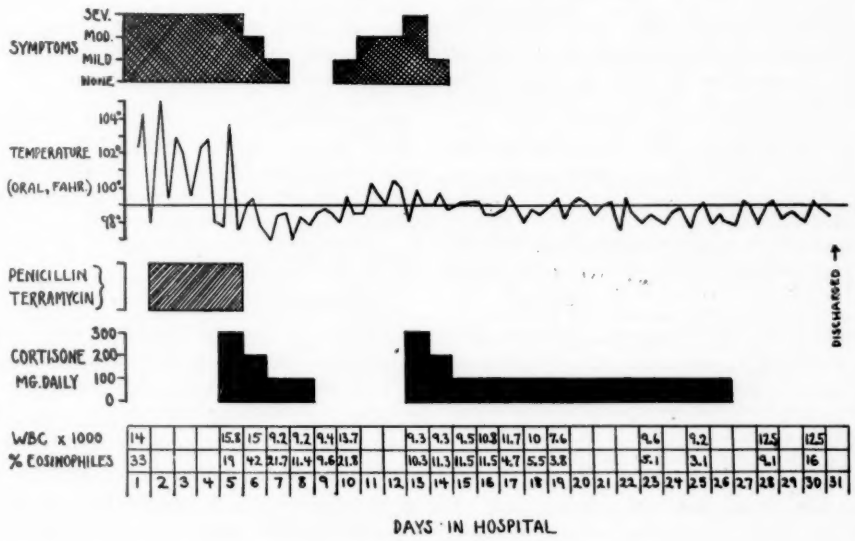
An electrocardiogram on the second hospital day showed a vertical heart position with clockwise rotation, low voltage of QRS complexes in all leads, and diphasic to shallowly inverted T waves in leads reflecting the epicardial surface of the left ventricle (AVF, V-7, and V-8). These changes were interpreted as compatible with trichinous myocarditis. A second tracing taken 6 days later showed normal findings except for a flat T wave in AVF. Later electrocardiograms taken on the 16th and 22nd hospital days were within normal limits.

A muscle biopsy was obtained on the 8th hospital day from a tender area in the right quadriceps. Microscopic examination of stained sections showed numerous foci of inflammatory cells including varying numbers of eosinophils. Hyaline degeneration and fragmentation of muscle fibers were noted in some areas. One section revealed a particularly large inflammatory focus containing an S-shaped portion of a trichina, without any definite capsule formation. These findings were felt to be indicative of recent infestation. A second muscle biopsy taken 13 days later again showed numerous inflammatory foci and portions of trichinae with beginning encapsulation. Comparison with the initial biopsy showed no improvement in the inflammatory reaction, but fewer eosinophils were present in the second specimen.

COURSE IN HOSPITAL. The patient's progress is diagramatically illustrated by the accompanying chart (Fig. 1). A clinical diagnosis of trichinosis was made, and in view of the severity of the patient's illness it was decided to consider cortisone treatment after a suitable control period. On the day after admission, a trial of combined antibiotic therapy was begun with 600,000 units of procaine penicillin intramuscularly every 12 hours and 0.5 gm. of terramycin orally every 6 hours. These medications were continued for 4 days, without any evident benefit. The patient continued to complain of severe muscle aching, headache, drowsiness, cough, chills, and profuse perspiration. The temperature graph showed daily peaks ranging between 103° and 105° F.

FIGURE I

TRICHINOSIS TREATED WITH CORTISONE



Cortisone was started on the 5th hospital day, with intramuscular injections of 100 mg. every 8 hours for 3 doses, followed by two 100-mg. doses at 12-hour intervals, and then 100 mg. daily for the next 2 days. A dramatic fall in temperature ensued, with concomitant clinical improvement. There was considerable amelioration of symptoms after the first day of cortisone therapy, and after 48 hours the patient was asymptomatic except for persist-

ence of slight cough and minimal muscular soreness. At this time he appeared alert and cheerful, and his general appearance had changed remarkably for the better.

In order to furnish evidence that this improvement was related to the treatment being given, cortisone was discontinued upon the completion of a 4-day course, and the patient was carefully observed for reactivation of his disease. Approximately 40 hours later he began to complain of increasing diffuse muscular aching, followed by severe headache, drowsiness, sweating, and feverishness. The oral temperature, which had been entirely normal for 3 days, rose to 99.4° F. on the 10th hospital day, and to over 100° F. the next two days.

Although the rise in temperature was only moderate, there was rapidly increasing deterioration of the patient's general condition, until on the 13th hospital day it was deemed unwise to postpone further the resumption of cortisone therapy. The same dosage schedule was employed, administering 300 mg. during the first 24 hours, followed by 200 mg. in the second 24 hours, and thereafter by daily injections of 100 mg. On this occasion cortisone was continued for a total of 14 days. The patient's symptoms and general appearance again showed remarkable improvement in 24 hours, and he remained completely free of symptoms after the second day of therapy. The effect on the temperature curve was not as striking as previously; the temperature declined to normal within 48 hours, but there was subsequent recurrence of occasional low grade elevations to 99.2° or 99.4° F.

Frequent blood counts failed to demonstrate any spectacular fall in the number of circulating eosinophils. The first course of cortisone produced a more or less gradual decline in the total white cells and proportion of eosinophils, until on the 9th hospital day the total white cells numbered 9400 per c.mm., with 9.6% eosinophils. Coincident with the return of symptoms after cortisone withdrawal, the total white cell count rose to 13,700, with 21.8% eosinophils. During the second course of cortisone, the fall in eosinophils was even less striking, and lagged considerably behind the clinical response. Following the final termination of cortisone therapy, the white cells and eosinophils again rose, although on this occasion there was no recrudescence of symptoms.

Consideration was given to increasing the dose of cortisone during the second phase of treatment, to learn whether higher dosage might eradicate the occasional low grade fever, and to observe the effect on eosinophil counts. However, this was not done in view of the fact that the patient remained clinically well, and because of the fear of provoking complications in a patient with a history of duodenal ulcer and psychoneurosis. The amounts of cortisone which were employed here produced no evident ill effects.

Skin tests with 0.02 cc. of trichinella extract (Lederle) were repeatedly negative for immediate or delayed reaction on 4 occasions from the 2nd to the 27th hospital days. However, the first two tests were at a comparatively early stage of the disease, and the latter two were done after the patient had been placed on cortisone. Since it was felt that cortisone might have altered the result, a skin test was repeated 4 days after discharge (9 days after cortisone was discontinued), at which time a positive immediate reaction was finally obtained.

The latter part of the patient's hospital stay was uneventful. The blood pressure remained low for about 3 weeks after admission, averaging about 94/50, and thereafter rose to a more normal level of 120/70. The biopsy sites healed normally. The patient was discharged on April 21, 1951, 5 days after the conclusion of cortisone therapy. No symptoms of trichinosis recurred during a follow-up period of 1 month.

Discussion. Although trichinosis is in many instances a mild and self limited disease, its potential severity is indicated by a mortality rate of approximately 6%[2] and the fairly frequent occurrence of serious complications or sequelae. Treatment has hitherto been largely supportive, since various therapeutic agents tried in the past have not proved to be of established value. Inasmuch as no other clearly effective therapy is available, it is important to examine the result of cortisone treatment in the patient reported herein.

It appears reasonable to conclude that cortisone effectively suppressed the manifestations of active disease in this patient. After a preliminary control period, striking improvement occurred during a 4-day course of cortisone therapy. This was followed by clinical relapse after withdrawing the drug for the purpose of establishing a second control period. The resumption of cortisone treatment again appeared

to be of remarkable benefit. On this occasion cortisone was continued for 14 days, following which the patient remained asymptomatic.

The mechanism by which cortisone acted in this case is a matter of conjecture. Available knowledge concerning the effects of cortisone and ACTH in other disease states seems to indicate that these agents act by altering tissue reactivity in some obscure manner. Studies of their efficacy in bacterial infections[5,6] have shown the production of clinical remissions despite the continued presence of viable microorganisms in the blood stream and other sites. Although signs of active disease may be suppressed, there is evidently no bactericidal effect, and in general the disease tends to run its course (perhaps in a rather inconspicuous manner) unless additional therapy of more specific nature is employed. Reasoning by analogy, a similar mechanism may be postulated in this instance, namely, an alteration in host reaction to the invading trichinae, without any direct effect on the parasites.

The lack of any striking reduction of circulating eosinophils was of interest, and indicated that the eosinophil response could not be used here as a measure of cortisone effectiveness. Absence of correlation between clinical response and changes in eosinophil counts have been previously noted for both cortisone and ACTH[4], but in these instances the eosinophil counts were at low normal levels before the start of therapy. Markedly elevated eosinophil counts have been dramatically reduced by ACTH in Loeffler's syndrome[3] and eosinophilic leukemia[1], and to a much lesser degree in tropical eosinophilia[3]. However, there is need for more data on the effect of cortisone and ACTH in eosinophilia due to parasitic infestations.

Summary and Conclusions. 1. Cortisone therapy appeared to be of striking benefit in a moderately severe case of trichinosis.

2. Further clinical trials of cortisone and ACTH are warranted in this disease.

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NEOMYCIN IN THE TREATMENT OF HUMAN AMEBIASIS

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In 1949 it was demonstrated that aureomycin is an effective amebicidal agent *in vitro* and *in vivo*[12,13]. Subsequently, these observations were confirmed by numerous investigators[1,7,14]. Inasmuch as this was the first instance of an antibiotic being clinically effective in human amebiasis, it stimulated an investigation into the possible effectiveness of other similar preparations.

Conn[2] treated 6 patients having amebic infections with chloramphenicol and reported a 50% cure rate. Others, however, have stated that this agent is of no value in human amebiasis[14, 17]. Most and Van Assendelft[15] found terramycin to be quite effective in amebic infections, but Shookhoff[17] observed less favorable results. Of 55 cases treated with bacitracin, 17 failures were reported by Most[14]; while in another series of 22 patients who received this therapeutic agent, recurrence was noted in 5 instances[17]. In any consideration of the role of antibiotics in amebic infections it should be recalled that Hargreaves, in 1945, pointed out that penicillin is of value in many cases of severe amebiasis[8]. After its use *E. histolytica* persists in the stool, but the healing of amebic ulcerations in the intestine may be greatly aided by the elimination or reduction of secondary bacterial infection.

It was decided to investigate the action of neomycin*, a recently developed antibiotic, in amebiasis because of its described alteration of the intestinal bacterial flora[4]. Shortly after this study was begun, Kadison and his associates reported that neomycin is amebicidal *in vitro* in concentration of 4.7 units per cc. of medium[10].

Neomycin was discovered in 1949 by Waksman and Lechevalier[19]. It is produced by a species of *Streptomyces fradiae* which is present in soil. Therefore, it is closely related to streptomycin and streptothricin. This antibiotic is a basic compound which is most active in an alkaline pH, is soluble in water, and is thermostable. It is effective against numerous Gram-negative and Gram-positive organisms. Of especial importance is the fact that it is active against streptomycin-resistant and streptomycin-sensitive organisms. It possesses marked *in vitro* activity against numerous forms of *Mycobacterium tuberculosis*. Recent inestigations have indicated that it is effective *in vitro* against *Salmonella typhosa* and *Pseudomonas* and *Proteus* organisms

* We are indebted to Dr. Lawrence W. Smith of Commercial Solvents Corp. for the neomycin employed in this study.

but has little action against *Clostridium*[10].

While only slight toxicity to neomycin was observed in mice and Macaccus monkeys, lesions in the renal cortex were produced in guinea pigs[11,18]. Felsenfeld and his associates reported that in man this antibiotic is excreted primarily through the kidneys[6]. The administration of intramuscular neomycin to patients has produced the following toxic effects in certain cases: complete deafness, temporary impairment of hearing, elevation of the blood non-protein nitrogen, microscopic hematuria, and albuminuria[4,10]. Therefore, it is necessary to be most cautious in its use. Poth and his associates employed the oral form of neomycin in 100 cases and observed only minimal toxicity[16]. Therefore, we decided to administer only the oral type of this antibiotic.

Material and Method. A strain of *E. histolytica* isolated from a case of acute amebic dysentery was employed in sensitivity studies with neomycin. Cultures were maintained in Nelson's egg yolk alcoholic extract medium. For these *in vitro* studies, neomycin was introduced into cultures in amounts ranging from 100 to 1,000 units per cc. of overlay. At the end of 48 hours, no amebae were present in any tube containing 500 to 1,000 units of neomycin per cc. and their number was greatly reduced in all tubes containing this antibiotic. The control cultures in every instance were strongly positive at 48 hours. While the bacterial flora was decreased in the tubes having neomycin, it was not significantly diminished in those tubes containing 500 units or less of neomycin per cc. of overlay. These *in vitro* sensitivity studies were repeated on 2 occasions with similar results.

In every case included in this series, the diagnosis of amebiasis was established by the demonstration of *E. histolytica* in fresh saline and iodine preparations and in culture on Nelson's egg yolk alcoholic extract medium. With the exception of 1 patient who was severely incapacitated as the result of a previous cerebral thrombosis, all patients were sigmoidoscoped prior to treatment. In only 1 instance were ulcerations of the intestine observed (Case 1). Before instituting therapy, the following laboratory procedures were obtained: white blood cell count, differential leukocyte count, hematocrit, urinalysis, blood non-protein nitrogen, blood urea nitrogen, total and fractional plasma protein, bromsulfalein retention, prothrombin time, cephalin-cholesterol flocculation, and the 1 minute and total serum bilirubin. After the beginning of treatment, a urinalysis was obtained daily, a blood non-protein nitrogen and a blood urea nitrogen every second day, and a total white blood cell count every fourth day. The liver function studies were repeated at the midpoint of treatment and again 24 hours after therapy was concluded. Stools were examined for amebae each day during therapy, and immediately thereafter, until at least 10 negative specimens were obtained. No stool was reported as negative for *E. histolytica* until it had been examined by fresh saline and iodine preparations, by iron hematoxylin stains, and by culture on Nelson's egg yolk alcoholic extract medium. During neomycin therapy fecal specimens were examined bacteriologically by aerobic and anaerobic methods. In 2 instances no bacteria were demonstrated in the stool during the last 48 hours of treatment. In every case there was a marked increase in the number of yeast cells in the feces while the patient was receiving neomycin. The most resistant organisms in the stool were *Bacteroides* and *Clostridium*. In 2 cases *E. coli* persisted though in reduced numbers.

Eight patients having mildly symptomatic amebic colitis were included in this investigation. Four were males and 4 were females; 6 were colored and 2 were white; the age of these patients ranged from 25 to 74 years. In 1 case acute rheumatic fever was present as well as amebic colitis. Because of the possibility of toxic reactions, all patients were hospitalized. Each case was observed initially and every third day by the otolaryngology resident to detect any auditory or vestibular dysfunction. Post-therapeutic hospitalization was continued until at least 10 stools free of amebae had been obtained. This permitted clinical observation for delayed toxic manifestations and tended to reduce the possibility of reinfection with *E. histolytica*. In this manner, neomycin could be more accurately evaluated as an amebicidal agent. Before releasing a patient from the hospital, efforts were made to eliminate the possibility of amebiasis in members of the immediate family. Every patient was re-examined in the Medicine Clinic of the John Gaston Hospital 1, 2, and 3 months after the completion of treatment. On each of these occasions, 3 stools specimens were studied for the presence of patho-

genic amebae. In addition to *E. histolytica*, 6 patients were found to harbor *E. coli*, and in 1 instance both *E. coli and E. nana* were present before treatment.

Results. The first 6 cases in this series received 50,000 units of neomycin orally every 3 hours for 1 day. Thereafter, they were given 50,000 units every 6 hours until a total of 1,600,000 units had been received. This required 7 days of treatment. Three of these cases have remained asymptomatic and free of amebae for 3 months. The remaining 3 cases revealed *E. histolytica* in their stools 6, 11, and 14 days after neomycin therapy was completed. Inasmuch as none of these patients had been out of the hospital and since all were on different wards, there was little possibility of reinfection. Of practical interest is the fact that these patients had 6, 8, and 12 negative stools after treatment before revealing *E. histolytica*. One of these patients had been retained in the hospital because of a subsiding episode of acute rheumatic fever; otherwise, he would have been discharged after 10 negative stools had been observed, and there would have been a possibility that the reappearance of amebae represented a reinfection. This emphasizes the importance of multiple, intermittent stool examination in possible cases of amebiasis.

Those 3 patients who were found to harbor *E. histolytica* after neomycin therapy were retreated. However, 3 times as much medication was administered during the second course of treatment. Fifty thousand units of oral neomycin were given every 3 hours until the total amount received was 4,800,000 units. This required 12 days. Since their second course of neomycin, all of these patients have been asymptomatic and free of amebae for 3 months. Two additional patients having amebiasis received 4,800,000 units of neomycin in the course of 12 days and have been free of amebae for 1 month.

In only 1 case in this series were significant toxic effects noted. In this instance (Case 2), the blood non-protein nitrogen and the blood urea nitrogen rose from 30 and 11.4 mg. per 100 cc. to 64 and 18 mg. per 100 cc., respectively. Also, a 3 plus and 4 plus proteinuria appeared. However, 72 hours after neomycin was discontinued the blood chemistry and urine findings were again within normal limits. Three patients in this series noted mild, painless diarrhea ranging from 3 to 5 semi-liquid stools per day; and 2 others observed slight, very transient nausea shortly after the ingestion of neomycin. In no instance did vomiting occur. Three patients noted no side effects.

Two cases of amebiasis treated with neomycin are briefly summarized as illustrations of treatment.

Case Reports. CASE 1. P.W., a 62-year old colored male, entered the John Gaston Hospital on March 13, 1951, with the complaints of anorexia for 6 months, "heart burn" after meals for 4 months, and intermittent bouts of mild diarrhea for 4 to 5 years. Examination revealed slight pallor of the mucous membranes and minimal tenderness on deep palpation over the region of the cecum. Sigmoidoscopy disclosed multiple, small, discrete punched-out ulcers in the rectosigmoid region. Material from these lesions as well as routine stool specimens disclosed *E. histolytica* and *E. coli*.

On March 14, neomycin therapy was instituted, using 50,000 units orally every 3 hours for 1 day and then the same amount every 6 hours until the total amount was 1,600,000 units. This course of treament required 7 days. After 48 hours the stools became persistently free of amebae. No toxic effects from the antibiotic were noted and the patient was discharged after 10 negative stools had been obtained. One week after completion of treatment, sigmoidoscopy revealed almost complete healing of the intestinal ulcers. When re-examined 1 month later in the clinic, the patient showed no evidence of amebic ulcerations in the rectosigmoid region.

This patient has been observed for 3 months since treatment and has remained asymptomatic. Seventeen stool specimens have

been negative for *E. histolytica* and *E. coli*.

Laboratory data: Total leukocyte counts ranged from 8,640 to 6,700 with repeated differential determinations being within normal limits; hemoglobin values were 12.5 to 13 gm.; hematocrit ranged from 36 to 39%; repeated urinalyses were within normal limits; blood non-protein nitrogen was from 28 to 34 mg. per 100 cc. with the blood urea nitrogen from 12 to 13 mg. per 100 cc.; the prothrombin concentration was persistently 100%; cephalin–cholesterol flocculation tests were from 0 to plus 1 at 24 hours; 3 determinations of the bromsulfalein retention (5 mg. per kg. of body weight in 45 min. intravenously) were 0 to less than 5%; total plasma proteins were from 6.8 to 7.4 gm. with a persistently normal ratio of albumin to globulin; the total serum bilirubin was 0.4 to 0.6 mg. per 100 cc. with the 1 min. value being persistently 0.1 mg. per 100 cc.

Case 2. M. M., a 46-year old colored female, was admitted to the Medical Service of the John Gaston Hospital on April 2, 1951. A diagnosis of amebic colitis had previously been established in the Medicine Clinic. The only complaint was vague generalized abdominal discomfort associated with a sensation of distension after meals. No significant findings were observed on physical examination. Sigmoidoscopic examination disclosed no evidence of amebic infection. Three stool specimens revealed *E. histolytica, E. coli,* and *E. nana.*

On April 4, neomycin treatment was begun using 50,000 units orally every 3 hours for 1 day, and then, the same amount every 6 hours until the total amount was 1,600,000 units. After 72 hours, the stools became free of all amebae. However, 6 days after treatment was completed and after 8 negative stool examinations, *E. histolytica* and *E. coli* were again present in the stools.

Therefore, therapy was reinstituted, using 50,000 units of oral neomycin every 3 hours until a total of 4,800,000 units had been given. This more intensive course of therapy required 12 days. Once more the stools became free of amebae after 48 hours of therapy. This patient has now been observed for 3 months since retreatment. She has remained asymptomatic during this period, and 18 stool specimens have been free of *E. histolytica, E. coli,* and *E. nana.*

After 48 hours on the second course of neomycin a mild, painless diarrhea developed consisting of 3 soft to semi-liquid stools per day. This persisted for 72 hours after the cessation of treatment. On the eleventh day of the repeated course of treatment, the blood non-protein nitrogen rose to 58 mg. per 100 cc. and the blood urea nitrogen to 17 mg. per 100 cc. Seventy-two hours previously the former had been 30 mg. per 100 cc. and the latter, 11.4 mg. per 100 cc. Inasmuch as treatment was to be concluded the following day, neomycin was continued and the blood non-protein nitrogen subsequently increased to 64 mg. per 100 cc. with the blood urea nitrogen rising to 18 mg. per 100 cc. Proteinuria, also, developed on the tenth day and increased to plus 3 on the eleventh day and plus 4 on the twelfth day. No hematuria was noted. Seventy-two hours after neomycin was discontinued, the urinalysis was within normal limits. Repeated urinalyses and blood chemistry determinations have subsequently remained persistently within the normal range. Aside from the abnormal findings discussed above, all laboratory results in this case were within normal limits.

Discussion. In the past 2 years the treatment of human amebiasis has undergone a marked transition. Extensive investigations have established that certain of the recently developed antibiotics are clinically effective in this widespread protozoan infection. These agents are much less toxic than emetine and the numerous arsenic and iodine compounds which have been routinely employed in the past as amebicidal agents. Furthermore, clinical results are equally as good in amebic colitis, amebic dysentery, and amebic hepatitis and are more rapidly attained.

The studies reported in this paper confirm the observation of Kadison and his associates that neomycin is amebicidal *in vitro*[10]. The results of its oral administration to 8 patients having amebic colitis also establish its efficacy *in vivo*. In 1 case included in this series, rapid healing of amebic ulcerations in the rectosigmoid followed the use of neomycin. A transient proteinuria and elevation of the blood nonprotein nitrogen and the blood urea nitrogen occurred in 1 patient. This was the only significant toxic reaction.

Aerobic and anaerobic bacteriologic studies demonstrated the broad antibacterial spectrum of this antibiotic. A striking increase in the number of

yeast cells was observed in the stools of every patient receiving neomycin. This phenomenon has frequently been observed with other antibiotics and has been believed by many to be an important cause of associated nausea, vomiting, diarrhea, and mucosal lesions[3,5,9].

Three of 6 amebic patients treated with 1,600,000 units of oral neomycin have remained asymptomatic and free of amebae for 3 months. The remaining 3 cases revealed recurrence of infection and were retreated using 4,800,000 units; these have been observed for 3 months since the second course of therapy and no evidence of amebiasis has been noted. Two additional cases treated for 12 days with 4,800,000 units of neomycin have been free of *E. histolytica* for 1 month.

This study emphasizes the importance of repeated intermittent stool examinations in possible cases of amebiasis, for 1 patient passed 12 negative stools before *E. histolytica* was demonstrated. The exact mode of action of neomycin in human amebiasis is not clear. Whether its therapeutic effect is due primarily to a direct action on *E. histolytica* or whether it exerts an indirect amebicidal action by altering the intestinal bacterial flora is yet to be determined. Perhaps there is a combination of both mechanisms. Bacteriologic examinations in these 8 cases revealed a striking reduction in fecal bacteria; however, *in vitro* sensitivity studies disclosed that amebae were destroyed prior to a significant reduction of the bacterial flora.

Summary. Neomycin is an effective amebicidal agent *in vitro* and *in vivo*. Further clarification of its toxicity, however, will be necessary before it can be used indiscriminately in the treatment of human amebiasis.

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THE INFLUENCE OF LOW-FAT DIET ON BLOOD LIPID LEVELS IN HEALTH AND IN MULTIPLE SCLEROSIS*

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EPIDEMIOLOGIC studies[20,22] have suggested the possibility that the incidence of multiple sclerosis in different geographic areas varies directly with the amount (and type) of the fat intake. In an attempt to determine whether this relationship is one of cause and effect, or merely coincidence, a low-fat diet has been employed in this clinic during the past 3 years.‡ At the same time we have made a systematic study of the blood lipids in patients with multiple sclerosis and in apparently normal people while on their usual diets, and for long periods on diets containing from 20 to 50% of the fat normally consumed. These studies are reported in this paper.

Materials and Methods. The normal control subjects included laboratory personnel and friends of patients. Fifteen patients had well-established multiple sclerosis, but were ambulant and able to come to the laboratory once a week without breakfast to give blood samples. One patient had amyotrophic lateral sclerosis. Most of their diets were analyzed prior to their being placed on the low-fat regimen by listing the food they ate for 3 to 7 days. The average amount of protein, fat, and carbohydrate per day was then calculated. This was checked by questioning. After a control period which varied from 1 to 8 weeks, most of the patients and normal control subjects were placed on a diet containing 30 gm. of fat per day. Seven patients, during the first period of study, received only relatively saturated fats (milk and animal). During the follow-up period in these 7 patients, and during the entire period of the study of the 8 additional patients and of all the normal subjects, 10 gm. of vegetable or cod liver oil were substituted for 10 gm. of the saturated fat in the diet. Two patients received 50 gm. of fat for 3 weeks, and 3 others received 50 gm. of fat for about the first 3 months, before being placed on 30 gm. daily. All subjects received 60 to 90 gm. of protein and sufficient carbohydrate to prevent loss of weight. The diet was listed daily in a diary and this was checked by a dietitian at 2-week and 4-week intervals.

All blood specimens were collected after 12 or more hours of fasting and prevented from clotting by heparin. The plasma and cells were separated by centrifuging the blood for 30 minutes at 3400 r.p.m. Samples of plasma were analyzed for *total phospholipid* by the method of Fiske and SubBarow[6]; for *free and total cholesterol* by the method of Schoenheimer and Sperry[15], with changes suggested by Sobel and Mayer[17]; and for *total fatty acids* by Boyd's modification[2] of Bloor's method[1], precautions previously described being taken[23]. *Neutral fat* and *total lipid* were calculated from the values obtained for these 4 fractions. Extracts for total fatty acids and phospholipid determinations were made in a 3:1 mixture of alcohol:ether, according to the method of Boyd[3]. Extracts for cholesterol determinations were made in a 1:1 mixture

* Supported by the Multiple Sclerosis Society of Canada.

† This material was accepted by the Faculty of Graduate Studies and Research of McGill University in partial fulfillment of the requirements for the degree Master of Science. Present address of author: Corvallis, Oregon.

‡ Data to be published by one of us (R.L.S.).

of alcohol:acetone. All solvents were redistilled before use. In some instances samples of red blood cells were also analyzed by the same methods, with the additional step of diluting the cells with an equal quantity of distilled water before extraction as described.

Results. A. FASTING PLASMA LIPID LEVELS IN NORMAL SUBJECTS AND MULTIPLE SCLEROSIS PATIENTS CONSUMING THEIR USUAL DIETS. The average fat intake of our patients (Nos. 1 to 15) prior to beginning the diet was 90 gm. daily (range 55 to 150). The fat intake of the normal subjects (Nos. 17 to 20) was approximately 20 gm. higher. The average values and the range of values for the various plasma lipid fractions for 14 normal subjects and for 15 patients with multiple sclerosis are shown in Table 1. The values in these 2 groups are approximately the same for most fractions. The slightly higher neutral fat values for the patients with multiple sclerosis may or may not be significant.

Of 14 normal subjects, 8 were studied weekly over periods varying from 4 to 12 weeks. In each individual, the average value for each fraction was computed, as well as the average variation of each fraction from its mean. Similarly, 9 to 15 patients with multiple sclerosis were studied weekly over periods ranging from 4 to 9 weeks, and similar computations were made. The variations of the values for the individuals were then averaged and are shown in Table 2. There seems to be no significant difference in the variations of any lipid fraction from its mean between normal subjects and patients with multiple sclerosis.

TABLE 1.—PLASMA LIPID LEVELS IN SUBJECTS CONSUMING USUAL DIETS

	Normal Subjects 8 women, 6 men (43 det'ns.) mg./100 cc.		*Multiple Sclerosis Patients 5 women, 10 men (44 det'ns.) mg./100 cc.*	
Lipid Fraction	*Average*	*Range*	*Average*	*Range*
Phospholipid	214	177–268	218	176–272
Total Cholesterol	188	112–241	194	140–244
Free Cholesterol	59	43–82	56	39–72
Ester'd Cholesterol	129	68–169	138	101–167
Neutral Fat	107	37–157	136	86–257
Total Lipid	591	477–722	639	486–765

TABLE 2.—WEEKLY VARIATIONS OF PLASMA LIPID LEVELS IN SUBJECTS CONSUMING USUAL DIETS

	Normal Subjects 4 women, 4 men mg./100 cc.		*Multiple Sclerosis Patients 4 women, 5 men mg./100 cc.*	
Lipid Fraction	*Average*	*Range*	*Average*	*Range*
Phospholipid	9	6–14	9	4–15
Total Cholesterol	12	5–17	12	6–24
Free Cholesterol	5	4–7	5	2–7
Ester'd. Cholesterol	11	6–17	8	3–17
Neutral Fat	32	20–48	26	8–40
Total Lipid	46	16–74	36	10–59

B. FASTING PLASMA LIPID LEVELS IN NORMAL SUBJECTS AND MULTIPLE SCLEROSIS PATIENTS ON LOW-FAT DIETS. In Tables 3, 4, and 5 are recorded the lipid levels for normal subjects (Nos. 1, 2, 3, and 4) and for all patients (Nos.

5 to 20) for the period prior to dieting, and also the changes in these levels (expressed in mg. + or −) which occurred during the period of the low fat diet. In the normal subjects and in the 15 patients with multiple sclerosis (Nos. 5 to 19) the phospholipid and cholesterol levels both decreased together on the low-fat diet to reach their lowest levels at an average of 5 weeks after institution of the diet. Studies in 9 of the patients made 5 to 13 months later indicated that the reduction in cholesterol was maintained. The phospholipid, however, had a tendency to return to the pre-dietary level.

The early changes in the neutral fat fraction were variable. In 9 of the 19 subjects (both normals and patients) there was no consistent change in the neutral fat. In 5 others, the first change was a rise and in the remaining 5 it was a decrease. There seemed to be no consistent difference between patients with multiple sclerosis and our normal subjects. The total lipids, which reflect a balance of all these fractions,

TABLE 3.—FASTING PLASMA LIPID LEVELS IN NORMALS (SUBJECTS 1–5) AND PATIENTS WITH MULTIPLE SCLEROSIS (SUBJECTS 6–9) ON LOW-FAT DIETS

Subject	Control Period (weeks) 1	2	3	4	5	6	7	8	9	Aver. values	Dietary Period (weeks) 1	2	3	4	5	6	7	8	9	10	11
1. Jy							199		239	219	**+17**	−21			−64	−37		−18			
							177		197	187	**+15**	−19			−32	−33		−16			
							67		69	68	68	71			70	68		64			
							61		22	42	**+34**	**+106**			**+101**	**+101**		**+70**			
2. Wr						199	189	182	208	195	−11	−26	−30	−17	−30	−22	−17	−1	−18	−10	−11
						185	168	165	192	178	−25	−61	−18	−23	−42	−18	−16	−25	−25	−30	−35
						75	73	74	71	73	70	74	66	68	67	70	71	71	69	64	69
						102	139	97	144	121	**+24**	−4	−66	−61	−42	−12	−72	−79	−59	−21	−3
3. Mn S				214	233	210	216	199	199	212	−22	−3	−16	−30	−24	−8	−20	−38	−17	−32	
				182	232	199	165	184	203	194	−21	−6	−26	−31	−33	−5	−19	−10	−18	−23	
				69	71	70	68	71	67	69	68	70	69	69	69	72	69	70	73	70	
				137	191	218	125	113	92	134	−9	0	−11	**+30**	−3	**+61**	**+31**	−2	−23	**+14**	
4. Mn J			197	196	175	198			197	195	−24	−33	−42	−44	−33	−41	−45	−25	−48	−32	
			176	186	176	165			178	176	−32	−45	−43	−55	−53	−50	−62	−41	−46	−48	
			69	70	73	72			67	70	67	70	71	69	70	69	74	71	70	70	
			130	159	125				84	125	−26	−41	−16	−34	**+59**	**+15**	**+22**	**+15**	−14	−15	
5. Py*						Attack	211	190	180	197	−32	−23	−13	−1	**+7**	**+1**	**+7**	−7			
							208	199	162	190	−45	−29	−34		−13	−19	−16	−33			
							73	75	69	73	70	70	67		72	70	73	70			
							175	148	79	134	−63	−13	−10	−12	−69	−51	−55	−41			
6. Wt				168	185	170	183	175	165	176	−9	**+3**	−21	−6	−16	−7	**+3**	**+3**			
				151	155	163	162	182	147	160	−10	−4	−13	−25	−10	−21	−11	−24			
				74	65	71	69	68	69	69	67	68	71	64	71	66	69	70			
				176	160	46	128	80	125	119	**+3**	**+23**	−39	**+33**	**+83**	**+10**	**+43**	**+17**			
7. So					272	260	261	283	286	272	−4		−57	−57	−42	−35	−50	−39	−34	−55	
					249	232	220	240	238	236	**+1**	−57	−63	−57	−48	−44	−44	−46	−52	−41	
					71	70	72	70	71	71	70	70	69	71	69	71	68	69	71	68	
					148	158		131	141	145	**+18**	−130	**+68**	−31	−31	−36	**+9**	**+14**	**+25**	−3	
8. Fx	190	205	185	175	143	166	170	174	202	179	**+6**	−7		0	**+2**	−1	**+5**	−2	−9	−16	
	149	183	172	132	100	124	132	122	181	144	0	−4		−24	−4	−21	**+10**	−16	−23	−31	
	68	68	68	69	66	70	71	70	76	70	69	73		68	68	69	71	70	70	65	
	102	117	50	65	40	85	117	128	72	86	**+17**	**+7**		−6	0	−22	**+7**	−4	**+26**	**+53**	
9. Cn					243	238	234	261	247	245	−13	−21	−24	−12	−23	−44	−41	−41	−41	−34	−51
					226	207	207	230	223	219	−15	−35	−35	−31	−33	−53	−49	−48	−58	−43	−60
					74	72	72	72	72	72	70	70	69	68	69	68	70	70	63	69	69
					146	117	142		117	131	**+20**	**+53**	−4	**+16**	−24	−6	**+66**	**+37**	**+73**	**+12**	**+74**

* Fat consumption was 50 gm. daily during first period of diet. Fat consumption was 30 gm. daily thereafter.

Times, pertinent to this study, at which patients had an exacerbation of their disease are shown by the word ATTACK.

For each subject, the figures in the top row in Tables 3, 4, and 5 are values for phospholipid; figures in the second row are values for cholesterol; the third row of figures shows percentage of total cholesterol present as esters; the fourth row of figures gives values for neutral fat.

During the pre-dietary period, actual levels are shown. During the dietary period, variations from the average pre-dietary levels are shown. The negative sign indicates values which were less than the average pre-dietary level. The positive sign indicates values which were greater than the average pre-dietary level. The positive values are indicated in **bold face type** to emphasize the infrequency of their occurrence, particularly in the cholesterol and phospholipid fractions, and to emphasize the fact that, for neutral fat, positive values tend to occur in short series of 3 or 4 consecutive weeks, followed by a series of negative values.

TABLE 4.—FASTING PLASMA LIPID LEVELS IN PATIENTS WITH MULTIPLE SCLEROSIS (SUBJECTS 10–15) ON LOW-FAT DIETS*

Subject	Control Period (weeks) 6	7	8	9	Av. values	Dietary Period (weeks) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
10. Pt				245		−43	−29	−31	−35	−7		−9				+4	−27	−21	−16	−29	−41	−1		−24	−36
				220		−61	−38	−39	−44	−34		−52				−8	−28	−37	−31	−55	−48	−30		−41	−51
				74		66	75	69	63	73		70				69	74	72	68	66	66	70		72	69
				118		−21	−2	**+93**	**+84**	**+74**		**+57**				**+66**	−11	−34		−12	−3	−26		−72	**+17**
													Attack												
																						19	20	21	22
11. He	198	229	220	206	213	−17	−12	**+27**	−16	−15	−3	**+8**										−21	−3	−11	−21
	176	198	188	175	184	−19	**+8**	**+4**	−12	−14	**+1**	−4										−26	−2	−11	−26
	69	65	72	65	68	68	67	70	69	65	69	69										70	71	69	68
	123	174	161	121	145	**+14**	**+51**	−105	**+56**	−11	**+27**	−33										−22	−30	−31	−10
12. Rn	226	258	265	250	250	−11	−26	−15	−20	−23	−10	−11	−20									−18	−11	−14	−12
	222	232	265	257	244	−12	−31	−4	−3	−25	−18	−28	−30									−25	−26	−28	−22
	71	72	72	68	71	67	68	70	71	71	70	70	72									72	70	74	71
	79	127	44	93	86	**+5**	**+51**	**+41**	−32	−11	−9	−26	−11									**+21**	**+45**	**+30**	**+36**
																						23	24	25	26
13. Ky	222	213	215	222	218	−4	−3	**+5**	**+7**	**+12**	**+9**	−4	**+34**	**+12**	**+10**	−3						**+16**	**+8**	**+17**	**+7**
	176	182	187	195	185	−39	**+7**	**+19**	−3	−3	**+19**	**+2**	**+31**	**+27**	**+4**	**+6**						**+10**	**+1**	**+8**	−46
	72	72	71	69	71	66	73	69	66	68	69	68	68	70	70	71						70	69	70	68
	170		91	116	126	−1	−66	−63	−97	**+21**	**+4**	−54	**+29**	−13	−35	−39						−5	−2	**+7**	**+58**
14. Wr	210	230	199	222	215	−33	−49	−40	−30	−35	−49	−26	−34	−8	−16	−20						**+3**	−9	−17	−13
	185	153	171	190	175	−45	−56	−31	−37	−37	−35	−20	−37	−27	−34	−34						−25	−35	−45	**+10**
	72	72	72	68	71	68	74	69	67	69	70	68	70	67	67	70						66	64	70	69
	89	175	97	150	128	**+34**	−45	−52	−35	**+5**	−38	−46	−48	−27	−29	−29						−25	−35	−33	**+4**
																						25	26	27	28
15. Jy	202	199	208	212	205	**+21**	−10	−8	−12	−30	−16	−17	**+23**	−1								**+11**	−5	**+15**	**+19**
	195	150	191	173	177	**+25**	**+1**	−9	−5	−9	−17	−15	**+4**	−10								−13	**+10**	**+16**	**+22**
	72	69	70	69	70	70	70	68	69	71	69	71	69	71								71	71	70	69
	204	102	33	128	117	−30	**+17**	−18	**+3**	**+24**	**+70**	−50	**+61**	**+36**								**+101**	**+20**	**+21**	**+36**

* The description of this table accompanies Table 3.

TABLE 5.—FASTING PLASMA LIPID LEVELS IN PATIENTS WITH MULTIPLE SCLEROSIS (SUBJECTS 16–20) ON LOW-FAT DIETS‡

Subjects	Control Period (wk.)	Dietary Period (weeks) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		61	62	63	64
16.	186	−17	−10	−1	+5	+3		+15				+6		+5	+13	−5				−3	−12	+8	+4
Fe	164	−15	−30	−5	+15	−5		−3				−1		+5	+23	+1				−23	−23	+21	−11
	74	79	79	79	75	72		70				70		74	72	70				68	71	71	71
	144	+60	+53	+15	+33	−19		+57				+32		−80	−15	−94				+32	−4	−6	+54
																51	52	53	54	55	56	57	58
17.	210	+5	−44	−6	−14	−2	−21	−16	+15	−2	−26	−20	−21	−8	−5	−15	+4	+4		−14	−7	−1	+13
Ww††	204	−12	−43	+2	+12	−22	−28	−20	−2	−21	−29	−27	−14	−9	−23	−7	−13	−17		+2	−15	−15	+4
	75	73	73	72	72	72	71	71	68	70	73	74	73	74	70	72	73	69		72	73	71	68
	133	+46		−92	−62	−48	−21		−22	−45	−82	−80	−85	−93	−65	−62	+50	−7		+10	+13	−33	−34
																31	32	33	34	35	36		46
18.	*226	−37	−31	−22	−24	−25	−29	−18	−31	−23	−26					−37	−17	−42	−18	−11	−10		−24
Pe†	184	−13	−16	−8	+4	+9	−7	−10	−9	−6	−32					−26	−23	−27	−16	−6	−2		−29
	69	70	67	68	68	69	69	71	70	70	66					67	67	70	68	70	72		67
	257	−76	−213	−177	−122	−167	−115	−168	−59	−202	−130					−77	−11	−107	−99	−86	−150		−159
																				51	52	53	54
19.	221	−5	−15	−16	−32	−26	−40	−33	−35											+11	+15	+21	+52
Sy†	210	−26	−33	−48	−53	−52	−56		−60											−23	−27	−73	+4
	70	69	67	68	70	70	70		69											67	71	67	70
	107	+67	−12	+45	+16	−59	−59	−23	−61											+111	+112	+226	+149
																				55	56	57	58
20.	177	−13	+1	+15	0	+1	+2	−6	−3	−23	−23	−10	−28	−8	−23					−12	+1	−7	+3
Hs**	130	−17	−13	+43	+18	+3	+4	+3	+4	−4	−28	−9	−17	−6	−3					−13	+10	+15	−3
††	71	79	70	70	69	73	69		69	67	69	70	69	73	69					66	69	69	71
	133	+3	−63	−114	−42	−82	−1		−112	−45	−36	−73	−56	−79	−110					−3	+7	−49	−44

‡ The description of this table accompanies Table 3.
* This patient had been fasting only 7 hours at the time this sample was taken. The plasma was turbid.
** Amyotrophic Lateral Sclerosis patient.
† Fat consumption was 50 gm. daily during first period of diet. Fat consumption was 30 gm. daily thereafter
†† Fat consumption was 50 gm. daily during first 3 weeks of dietary period. Thereafter it was 30 gm. daily.

fell in 11 cases, in 9 of which they reached their lowest points during the first 2 months. Studies of the neutral fat levels in 9 of the patients with multiple sclerosis made 5 to 13 months after institution of the diet indicated that there was no consistent change in this fraction after either short or long periods of dieting. One of these (Case 18) had a high predietary neutral fat (probably inadequately fasted) which makes all of his subsequent levels appear unusually low.

In 11 subjects, cyclic variations occurred in the neutral fat levels. These seemed to be independent of the diet, and might explain why in some patients the first response to the low-fat diet was an increase and in others a decrease in the neutral fat level. In addition, less marked cyclic variations were observed in the cholesterol and phospholipid levels of 10 subjects, and these were usually concurrent. In those subjects who also showed cyclic variations in neutral fat there was no apparent relation between cycles in neutral fat levels and cycles in cholesterol and phospholipid levels, except possibly in 4 subjects in whom there seemed to be a tendency for the neutral fat to maintain a reciprocal relationship to phospholipid and cholesterol.

In attempting to discern some pattern in the sequence of the lipid changes, comparisons were made of the time relationships between the lowest single determination of each fraction. These showed that there was no definite sequence of lipid level reduction in either the patients or normal subjects. In all subjects, the phospholipid and cholesterol levels tended to fall together, the average time interval between the lowest single determination of the 2 fractions being 1 week. In contrast, the average time interval between the lowest single determination of phospholipid and of neutral fat was 3 weeks.

In summary, plasma phospholipid and cholesterol levels tended to decrease during the early period of dieting, and this was often sufficient to cause a decrease in the total lipid level. Extension of the period of dieting did not seem to maintain lowered lipid levels, with the possibly significant exception of cholesterol. In connection with this observation regarding cholesterol levels, it is interesting to note that there was a reduction in the percentage of total cholesterol present in plasma in an esterified form. An average of 45 determinations, made before the low fat diet was instituted in 15 patients with multiple sclerosis, gave an average cholesterol-ester percentage of 71.0. An average of 54 determinations, made 6 to 11 weeks after the institution of the diet, gave a percentage of 69.5. In view of the fact that the standard deviation, as determined by us, using the Schoenheimer–Sperry method, was 1.6% for 14 determinations, this change may be significant. Subsequent studies of some of these patients after longer periods of dieting indicated that the reduction of the percentage of cholesterol esters was maintained. It is of interest, and possibly significant, that the percentage of cholesterol present as ester during pre-dietary periods in normal subjects was only 68.6, compared to the 71.0 found for the patients. In normal subjects this percentage did not change significantly with dieting.

C. Fasting Cellular Lipid Levels in Normal Subjects and Multiple Sclerosis Patients Before and During Consumption of Low-Fat Diets. Red blood cell lipid levels were determined in 3 patients and in 2 normal subjects, during a 4-week period on a normal diet and for 9 to 11 weeks on the low fat diet (30 gm.). Two months after the institution of low fat diets, the level of the total cellular lipids remained unchanged in 4 out of 5 of these subjects, and had increased slightly in the fifth.

However, there was some shift in the levels of the individual lipids; phospholipid levels fell in 2 out of 5 subjects, and neutral fat levels rose in 4 out of 5 subjects. The average values, and the range of values for red blood cell lipid levels, before and 2 months after institution of the low-fat diet, are shown in Table 6. Corresponding average values and the range of values for plasma lipids in the same 5 subjects during the same 2 periods are shown in Table 7. Comparison of these 2 tables shows that the range of values for each fraction of cellular lipids among these 5 individuals is smaller than the range of values for corresponding fractions of plasma lipids. This lends support to the idea that cellular lipids are an integral part of the cell structure. This is further supported by the fact that, although the total plasma lipid levels fell during dieting, the total cellular lipid levels remained essentially unchanged. It was also noted that, for any given individual, the cellular lipid levels remained almost constant, despite occasional large fluctuations in plasma lipid levels. The average variations of the cellular lipid levels are shown in Table 8, and it can be seen by comparison with Table 2 that the average variation of each fraction, except phospholipids, is less than that of the corresponding plasma lipid fraction.

D. Fasting Plasma Lipid Levels in One Patient with Amyotrophic Sclerosis. The 1 patient with this neurological disease (Case 20) exhibited no change in his plasma lipid levels while on a low-fat diet, which would distinguish him from either the normal subjects or patients with multiple sclerosis.

TABLE 6.—RED BLOOD CELL LIPID LEVELS BEFORE AND 2 MONTHS AFTER INSTITUTION OF THE LOW-FAT DIET IN 5 SUBJECTS

	Before Diet mg./100 cc.		*Two Months after Diet mg./100 cc.*	
Fraction	*Average*	*Range*	*Average*	*Range*
Phospholipid	386	364–402	379	364–397
Total Cholesterol	137	126–146	131	123–141
Free Cholesterol	134	124–143	130	123–139
Neutral Fat	65	43–82	91	76–107
Total Lipid	590	554–632	603	581–636

TABLE 7.—PLASMA LIPID LEVELS BEFORE AND 2 MONTHS AFTER INSTITUTION OF THE LOW-FAT DIET IN 5 SUBJECTS

	Before Diet mg./100 cc.		*Two Months after Diet mg./100 cc.*	
Fraction	*Average*	*Range*	*Average*	*Range*
Phospholipid	220	178–275	190	158–228
Total Cholesterol	195	140–240	158	127–190
Free Cholesterol	57	39–71	49	39–58
Neutral Fat	130	101–145	142	107–180
Total Lipid	637	486–772	562	469–662

Discussion. Our studies indicate that with respect to plasma and blood cell lipid levels, both during and before the consumption of low-fat diets, normal control subjects and patients with multiple sclerosis do not differ significantly. It seems likely that, if an abnormality were present in our patients, some significant deviation from the normal values would have been observed. The slightly higher fasting plasma neutral

fat levels in the patients are probably within the limits of variation to be expected in 2 small groups of subjects. This difference could be because our patients, although ambulatory, were not as active as the normal subjects, or because there is a slower removal of neutral fat from the blood of the patients. The possibility that the higher neutral fat levels are the result of the addition of lipids to the blood stream from degenerating nervous tissue seems unlikely, in view of the facts that the total amount of lipid being released from degenerating nervous tissue must be relatively small, and that even an alimentary lipemia after a very large fat meal is transitory.

TABLE 8.—WEEKLY VARIATIONS OF RED BLOOD CELL LIPID LEVELS IN SUBJECTS CONSUMING USUAL DIETS

	Before diet	
	mg./100 cc.	
Fraction	*Average*	*Range*
Phospholipid	10	6–15
Total Cholesterol	4	2–6
Neutral Fat	21	13–29
Total Lipid	23	12–31

Despite the fact that our diet contained a normal amount of cholesterol (0.7 to 1.0 gm. daily) we observed both a decrease in the total amount of the plasma cholesterol and a small decrease in the percentage of this material present in an esterified form. These observations confirm previous statements[8,9,11,12] that the plasma cholesterol levels in humans are independent of the intake of cholesterol. Changes in the cholesterol level similar to those observed by us during dieting were noted by Kempner[10] and others[5,16,19,25] using the rice diet, which they report contains no cholesterol. Since restricted fat intakes were utilized in our experiments as well as by the investigators using the rice diet, it would appear that a low-fat intake can itself cause a reduction in the plasma cholesterol level in humans. This observation was also made by Brown *et al.*[4], although others[7,13,24] found no correlation between fat intake and cholesterol levels. It is, perhaps, of clinical importance that the plasma cholesterol levels may fall when a diet containing 30 gm. of fat is consumed, since such a diet is more palatable than a fat-free diet.

Although Kempner stated that there was no change in the ratio of free to esterified cholesterol, his figures do show a change in this ratio of about the same order of magnitude as that observed by Watkin, Froeb, Hatch, and Gutman[25], by Starke[19] and by us. When Watkin *et al.* added a vegetable oil to the rice diet of 5 of their patients, the percentage of cholesterol esters returned to normal. In our patients with multiple sclerosis this disproportion took place despite the fact that all of our patients received 10 gm. of vegetable oil daily as part of their fat intake throughout all or the greater part of the dietary period. Our values for the percentage of total cholesterol in the esterified form in normal subjects are lower than have been reported by others[14,18] but were not changed by the low-fat diet.

Our observations of neutral fat are similar to those of Watkin *et al.*, and lead to the conclusions reached by earlier writers that the fasting plasma neutral fat levels have very little relationship to the amount of fat in the diet. The cyclic variation of neutral fat, which was often quite marked, and of cholesterol and phospholipid are of some interest. They can make interpretation of lipid levels very difficult, unless values over long periods are available. Watkin *et al.* found that in those patients in whom the cholesterol:lipid phosphorus ratio fell, neutral fat was observed to rise. In our group of 15 multiple sclerosis patients, this ratio

fell in 10 and did not change in 5. There was no correlation between the behavior of this ratio and the behavior of neutral fat levels in either patients or normal subjects. Thus, although the cholesterol and phospholipid levels tend to change together during the early period of dieting, there is a definite tendency for the ratio of cholesterol to phospholipid to fall subsequently. This is to be expected, if cholesterol levels remain depressed while phospholipid levels return to predietary levels.

It is of interest that, despite the absence of any clear relationship between the neutral fat levels in the fasting plasma and the amount of the daily fat intake, the tendency of chylomicrons to cluster *in vitro* after a fat meal is clearly increased by the consumption of a high fat diet (150 gm. daily for 1 or 2 weeks) and decreased by the consumption of a low fat diet (20 to 30 gm. daily for a similar period, Swank[21]). These tests also showed that the tolerance of the individuals for a fat meal, as indicated by the shape of the neutral fat curve, was decreased by the high-fat diet, but not changed by the low-fat diet (Wilmot[26]).

Many observations of patients with multiple sclerosis* have shown that after they begin the low-fat diet, there is a reduction of the amount of clustering in heparinized blood *in vitro* during the post-absorptive period. These observations indicate that a significant physical change in the visible neutral fat (chylomicrons) does result from a low-fat diet, even though this is not reflected in our chemical analyses. This may be because we were studying only fasting plasmas in which the number of chylomicrons is negligible. In other studies (Swank and Wilmot[23]), it has been shown that the lipid composition of the chylomicrons in the plasma of dogs consists of about 97% neutral fat and 3% free cholesterol. In fasting clear plasmas, practically all of the neutral fat is in solution (or invisible), but after a fat meal of 4 gm. per kg., the amount of the visible neutral fat (chylomicrons) averages 75% of the increase of this fraction in the plasma and approximately one-third of the total plasma neutral fat. The injection of small amounts of heparin intravenously into lipemic dogs usually causes a marked shift in the neutral fat from the visible form to the invisible form.

It is also of interest that the amount of clustering of the chylomicrons in the plasma after a fat meal in both humans and dogs is much greater after the consumption of butter fat than after the consumption of the much less saturated vegetable oils, or after cod liver oil and raw linseed oil (Swank[21]). The chemical analyses in these studies showed no significant differences, except that there seemed to be a delayed rise in the neutral fat after ingestion of the more unsaturated fats (Wilmot[26]). This difference was thought to be due to the less palatable nature of the unsaturated fats.

Summary and Conclusions. Fasting blood lipid levels were determined weekly for long periods in normal subjects and in patients with multiple sclerosis, both before and during the consumption of low fat diets (30 to 50 gm. of fat daily).

No essential differences were found between normal subjects and patients with multiple sclerosis with respect to either lipid levels or the response of lipid levels to the change in diet.

The effect on lipid levels of reducing the fat intake in both normal subjects and patients with multiple sclerosis was a temporary reduction of total lipid, caused chiefly by a reduction in phospholipid and cholesterol (primarily esterified cholesterol) levels. The reduc-

* Unpublished observations by one of us (R.L.S.)

tion in cholesterol levels was maintained, in those subjects followed, for periods up to a year after the institution of the low-fat diet, whereas the phospholipid tended to return to predietary levels.

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CEREBRAL MANIFESTATIONS OF ACUTE MYOCARDIAL INFARCTION

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It has long been recognized that cerebral manifestations may be present in acute myocardial infarction[7], yet it has not been sufficiently emphasized that central nervous system symptoms may be the sole presenting symptoms of this condition. Few of the writers, recognizing that the cerebral symptoms had a cardiac basis[1,2], have confirmed their impression or ruled out concomitant intracranial lesions by adequate neurologic examinations, electroencephalography, and necropsy.

While dyspnea commonly has been recognized as a sign of painless infarction[11], the presence of syncope, convulsions, hemiplegia, or coma seldom has led the clinician to suspect an underlying recent cardiac catastrophe. The purpose of this paper is to emphasize that cerebral manifestations may be the predominant symptomatology of acute myocardial infarction.

We cite 6 illustrative cases. With the exception of the patient mentioned in Case 2, who is living and well, all were derived from a series of 100 cases of acute myocardial infarction gathered from the autopsy files of the Cedars of Lebanon Hospital. A series of 100 cases with cerebrovascular accidents from the same source was also reviewed to determine the incidence of concomitant myocardial infarction.

Case Reports. Case 1. F. M., a 41-year old white male, was found unconscious. Subsequently he had repeated convulsive seizures confined to the head and right upper extremity. A fall during an attack produced contusions and subconjunctival hemorrhages. His first lumbar puncture showed only 70 mg. of protein and no cells. Electroencephalograms and a second lumbar puncture were negative. The clinical diagnosis was possible brain tumor. Eight days later an apical systolic murmur and rub appeared, which with serial electrocardiograms led to the diagnosis of acute myocardial infarction. The blood pressure was 110/70. No change in blood pressure or pulse was observed during the epileptiform attacks. At autopsy, infarction of the lateral wall of the left ventricle, stenosis of the left coronary artery, and recent thrombotic occlusion of the right coronary artery were the cardiac findings. The brain showed marked vascular congestion and moderate sclerosis of the arteries at the base. A small hemorrhage in the pons was not considered to be related to the clinical symptoms.

Case 2. C. K., an 85-year old hypertensive, mildly diabetic white woman with previous episodes of syncope, developed a transient right hemiplegia and aphasia following a fall. Her blood pressure dropped from 250/130 to 180/100. She had large bilateral periorbital hemorrhages with associated subconjunctival ecchymoses. The clinical diagnosis was possible fractured skull and cerebrovascular accident. Roentgenogram of the skull, however, showed only sclerosis of the carotid arteries. Serial electrocardiograms revealed the typical evolution of a recent infarction of the posterior wall of the left ventricle. Blood and urine sugar determinations were within normal limits. The final diagnosis was arteriosclerotic heart disease, recent posterior myocardial infarction, and cerebral arteriosclerosis. She recovered completely and at present is living and well.

Case 3. A. G., a 57-year old male, with hypertension and a history of transient left facial paralysis and left hemiplegia, became unconscious, following which he had a recurrence of the left facial paralysis and later a right hemiplegia. He became disoriented and incontinent before he died. Because of the purely cerebral signs, no electrocardiograms were taken. At autopsy there was a fresh myocardial infarction of the anterior wall of the left ventricle. The left anterior descending branch contained a recent antemortem thrombus. The right coronary artery showed an old atherosclerotic occlusion with recanalization and a mural thrombus over the scarred

area. The left cerebral hemisphere was somewhat soft and cystic. There were marked atherosclerotic changes but no evidence of fresh thrombus, hemorrhage, or embolus.

CASE 4. I. S., a 61-year old male, was admitted to the hospital in an unconscious state after complaining of dyspnea and chest pain. His blood pressure fell from 200/100 to 100/70, and a left Babinski sign was elicited. He continued in a stupor until he died a few hours later. The clinical diagnosis was cerebral hemorrhage, pulmonary edema, and hypertensive and arteriosclerotic heart disease. At autopsy there was a recent infarction of the lateral wall of the left ventricle and posterior part of the interventricular system. Examination of the brain showed only cerebral edema.

CASE 5. E. H., a 44-year old man with known hypertension, was admitted to the hospital on Mar. 11, 1949, with the diagnosis of hypertensive encephalopathy and possible coronary thrombosis. On Mar. 13 he became irrational and incoherent and developed generalized twitching and marked nuchal rigidity which led to the diagnosis of secondary meningismus. The spinal fluid examinations were within normal limits, as were the blood sugar and non-protein nitrogen determinations. He expired after an attack of Cheyne-Stokes respiration. At autopsy, the brain showed only a mild degree of arteriosclerosis but no focal lesions to account for the central nervous system symptoms. There was a recent occlusion of the descending branch of the left coronary artery.

CASE 6. Z. R., a 65-year old male, while being fluoroscoped for duodenal ulcer, complained of sudden headache, paresis of the right facial, arm, and leg muscles, weakness, and inability to talk. These disappeared completely within 30 minutes. Later slurred speech, drowsiness, and weakness of the internal rectus muscle with failure of upward gaze appeared. There was a positive Oppenheim sign on the left. His blood pressure fell from 110/70 to 80/50. The diagnosis was a thrombotic lesion of the midbrain, including part of the oculomotor nucleus on the right, and pyramidal tract involvement. Two days later, substernal pain and a blowing apical systolic murmur appeared. An electrocardiogram revealed the pattern of an old posterior and recent anterior myocardial infarction. The final clinical diagnosis was cerebrovascular accident and myocardial infarction. At autopsy, the posterior wall of the left ventricle was practically replaced by fibrous tissue. There was complete occlusion of the left coronary and circumflex arteries. The brain showed considerable atherosclerosis but no visible thrombosis, hemorrhage, or embolus. There was a suggestive area of softening in the left cerebral hemisphere.

Discussion. Five of the above patients were males, and the average age at death was 54 years. In Case 2, that of an 85-year old woman, the patient is still living and well. The most frequent neurologic findings were syncope and convulsions. They were usually repeated, intermittent, and fleeting. At autopsy, no evidence of cerebral thrombosis, embolus, or hemorrhage was found.

It is of interest to compare these findings with those of the 15 cases presenting both cerebrovascular accidents and recent myocardial infarction. They were derived from the same autopsy series; the data are given in the following table.

TABLE 1.—DATA ON 15 PATIENTS WITH COMBINED MYOCARDIAL INFARCTION AND CEREBROVASCULAR ACCIDENT

Case No.	*Age Sex*	*Time of Onset of Cerebrovascular Accident*	*Central Nervous System Manifestations*	*Survival Time after C.V.A.*	*Cerebral Lesions*	*Myocardial Lesions*	*Miscellaneous*
7. I. T.	71 F	14 days after infarct	Left facial weakness; right hemiplegia	2 days	Hemorrhage, left internal capsule, with infarction	Recent infarction of posterolateral wall of left ventricle and adjacent septum	Hypertension, auricular fibrillation Early carcinoma of the stomach, not suspected clinically Old rheumatic aortic and mitral valvulitis
8. M. M.	52 F	14 days before admission	Coma from onset	4 days	Thromboembolism with infarction of left cerebral hemisphere	Mural thrombus over recent infarction of apex of left ventricle and adjacent septu	Hypertension In coma since onset, following a dose of sleeping pills

TABLE 1.—DATA ON 15 PATIENTS WITH COMBINED MYOCARDIAL INFARCTION AND CEREBROVASCULAR ACCIDENT—(*Continued*)

Case No.	*Age Sex*	*Time of Onset of Cerebrovascular Accident*	*Central Nervous System Manifestations*	*Survival Time after C.V.A.*	*Cerebral Lesions*	*Myocardial Lesions*	*Miscellaneous*
9. A. L.	74 F	Coma 19 days after infarct Hemiplegia 21 days after infarct	Coma and right hemiplegia	2 days	Thrombosis with hemorrhagic infarction of left cerebral hemisphere	Recent infarction of the posterior wall of the left ventricle	Hypertension
10. S. W.	73 F	18 days after infarct	Right hemiparesis	3 days	Thrombosis of left middle cerebral artery with softening of left parietal lobe in region of internal capsule	Old anterior wall and recent posterior infarction of the left ventricle	Syphilitic aortitis with atheromatosis Auricular fibrillation Thrombosis of the renal and hepatic arteries
11. B. B.	65 F	3 hours after onset of pulmonary edema	Stupor, hemiparesis, coma	1 day	Arteriosclerosis with infarction of right parietal lobe	Recent infarction of the anterior wall of the left ventricle	Hypertension Diabetes mellitus
12. C. C.	66 F	28 days after infarction	Stupor, to coma from onset	6 days	Hemorrhage into basal ganglia with subarachnoid extension	Recent infarction involving papillary muscles of left ventricle	On Dicumarol Hypertension Diabetes mellitus Kimmelstiel-Wilson's disease
13. H. A.	60 M	16 days after infarction	Right hemiplegia	2 days	Thromoembolus with infarction of left frontal lobe and cerebral peduncle	Mural thrombus over recent infarction of posterolateral wall of left ventricle	Early infarction of kidney
14. M. G.	50 M	10 days after infarction	Left hemiplegia	4 days	Thromboembolism with hemorrhagic infarction of right internal capsule and basal ganglia	Mural thrombus over recent infarction of posterior wall of the left ventricle Rupture of the myocardium	Hypertension
15. L. C.	69 F	3 days after infarction	Right hemiplegia Coma Agonal convulsion	2 days	Thromboembolism of left internal carotoid, middle cerebral arteries. Multiple infarctions of left cerebral hemisphere	Mural thrombus over recent infarction of posterior wall at the base of the left ventricle	Auricular fibrillation Old healed rheumatic endocarditis
16. R. B.	71 F	0	0	0	Thrombosis of right middle cerebral artery	Recent infarction of the posterolateral wall of the left ventricle	Cerebrovascular accident not suspected clinically. Obscured by terminal acute pulmonary edema. Illness 5 days
17. S. B.	72 M	22 days after infarction	Left hemiplegia	2 days	Thromboembolus of right midcerebral artery with multiple infarctions of right cerebral hemisphere	Mural thrombus over infarction of the posterior wall of the left ventricle	Hypertension
18. A. K.	62 M	0	0	0	Old encephalomalacia	Recent infarction of the anterior wall of the left ventricle	No history relative to the cerebral findings. Autopsy. Death due to the myocardial infarction Diabetes mellitus
19. L. W.	31 M	Coma from onset	Coma, old right hemiplegia	0	Cerebral softening in left hemisphere	Mural thrombus over recent infarction of the apex of the left ventricle	Polycythemia vera with multiple thromboses. Death probably due to mesenteric thrombosis
20. J. R.	42 M	10 days postappendectomy	Coma	0	Embolic occlusion left carotid, anterior and midcerebral arteries	Mural thrombus over recent infarction of the apex of the left ventricle	Rheumatic heart disease Mitral stenosis Ball-valve thrombus in left auricle Auricular fibrillation Acute gangrenous appendix History of "saddle" thrombus
21. L. K.	60 M	4 years before infarction	Old left hemiplegia	0	Encephalomalacia	Recent infarction of the posterior wall of the left ventricle Rupture of left ventricle	Old history of subarachnoid hemorrhage and hemiplegia Death due to cardiac lesion

Cases 18 and 21 were discarded because there was no contemporary relationship between the cardiac and cerebral accidents. Cases 19 and 20 were eliminated because they were complicated by polycythemia with multiple systemic thromboses, and rheumatic mitral stenosis with a thrombus in a fibrillating auricle. The average age of the patients in the remaining 11 cases was 64.8 years. There were 8 females and 3 males. The most common neurologic findings were stupor or coma and hemiplegia or hemiparesis. When coma from the onset did not obscure the picture, the neurologic findings appeared from 3 hours to 28 days after the clinical onset of the myocardial infarction. Once present, they were permanent, and presaged the demise of the patient, usually within 4 days.

At autopsy, thromboembolism was found in nine cases. This term is used since the pathologic differentiation of cerebral thrombosis from embolization is often impossible. The inference of embolization was considered justifiable when cardiac mural thrombi or peripheral emboli, or both, elsewhere in the body were discovered. Five of the patients had mural thrombi overlying the myocardial infarction sites which could have been the source of cerebral emboli.

There were 2 cases of cerebral hemorrhage (Cases 7 and 12). In the latter, dicumarol had been given and was considered one of the causative fatal factors. With the more frequent use of anticoagulants, it will be of interest at a later date to determine whether hemorrhage will furnish a greater percentage of the cerebrovascular accidents complicating myocardial infarction.

In Case 16, the cerebrovascular accident was not suspected clinically but was discovered at autopsy. This is comparable to the 2 cases showing no neurologic signs described by Race and Lisa[10] in their study of combined acute vascular lesions of the brain and heart. Eight of their cases showed no cardiac symptoms. Similarly, Dozzi[5] found 12 instances of clinically unsuspected coronary thrombosis in a series of 107 cases of cerebrovascular accidents. In all our cases, however, the cardiac lesions were diagnosed clinically before postmortem examination. This may be due to the greater frequency with which electrocardiograms are taken now, as compared with 10 years ago. This does not deny the fact that the routine use of the electrocardiogram in cases of suspected cerebrovascular accident would reveal unsuspected myocardial infarctions.

Conversely, more complete and repeated neurologic surveys of patients with myocardial infarction, and portable electroencephalographic techniques made applicable to these critically ill patients, will uncover unsuspected cerebrovascular accidents. To this end, autopsy examinations of cases of myocardial infarction should include a routine head examination.

Since the original dissertation on the clinical recognition of coronary occlusion by Herrick[7], it has been recognized that general cerebral symptoms may be present in this condition. Before they can be attributed to the cardiac condition, however, the existence of associated cerebral hemorrhage, thrombosis, or embolization must be ruled out, either by clinical means as described above or by postmortem examination.

That syncope, coma, and convulsions may arise in acute myocardial infarction without cerebral hemorrhage, thrombosis, or embolus is demonstrated by Cases 1, 2, 3, 4, and 6. Cookson[4] found fainting and fits to be present in 15 of 200 cases of myocardial infarction, but a concomitant intracranial lesion was not ruled out, since none

of his cases came to necropsy. Bean and Read[2], however, presented both clinical and morphologic data of 8 cases in which there were symptoms of acute cerebral disease associated with infarction of the heart, and no clinical diagnosis of heart disease was made because the bizarre central nervous system manifestations obscured the picture. All their cases had cerebral arteriosclerosis and several showed fall in blood pressure. Lisa and Ring[9] found that in 5 of their 100 cases the clinical manifestations led to the diagnosis of the cerebral accident. In each case the brain, both on gross examination and section, showed no acute vascular lesion.

Generalized cerebral manifestations may be brought on by ischemia or anoxia secondary to diminished blood flow following a fall in blood pressure, particularly in patients with a background of cerebral arteriosclerosis. Behrend and Riggs[3] found coma, convulsions, and psychic disturbances in patients with lowered arterial pressure due to surgical shock. No thrombi, emboli, or hemorrhages were seen in the brains they examined. Kety and associates[8] found that temporary spinal sympathetic block with reduction of blood pressure in hypertensive patients may be associated with persistence of vasoconstriction in the brain and significant decrease in cerebral blood flow. Ferris, Capps, and Weiss[6] described syncope occurring following pulse slowing, followed by rapid arrhythmias and finally by a cerebral reflex, presumably arising from the heart, in which there was no fall in blood pressure or change in pulse rate. This latter must be invoked to explain the findings in Case 1, in which no changes in blood pressure and pulse were noted.

In acute myocardial infarctions any one or more of the previous conditions may be present. The concomitant existence of coronary and cerebral arteriosclerosis is frequent, as is a drop of blood perssure. There may be any type of arrhythmia or conduction defect. The hemodynamics are altered, and, with the advent of the cerebral manifestations, the heart may be completely overlooked as the site of the pathology.

These mechanisms, however, do not explain the focal neurologic findings, such as the hemiplegias which occurred in Cases 2, 3, and 6. There must be a segmental narrowing or arterial impairment in addition to the general cerebral ischemia to explain these symptoms arising from a sharply localized area. These 3 patients all had cerebral arteriosclerosis, and since the patchy distribution of this process is known, this postulation is not unlikely. In order to exclude completely this possibility, we must await more meticulous dissection of the entire cerebral arterial system, multiple microscopic sections, or injection of the vascular tree of the brain with radiopaque media, as has been done with the coronary system. Electroencephalograms taken at the time of hemiplegia might be helpful in localization of the affected area. Routine electrocardiograms in all cases with central nervous system symptoms would uncover more unsuspected acute myocardial infarctions.

Summary. Syncope, convulsions, coma, or hemiplegia may be the only presenting symptoms of acute myocardial infarction.

Six cases are presented in which central nervous system symptoms so dominated the clinical picture that the brain was suspected as the seat of the pathologic process, and the cardiac accident initially was overlooked. No evidence of cerebral thrombosis, embolus, or hemorrhage was found at autopsy.

Possible mechanisms to account for the cerebral symptoms on the basis of myocardial infarction are discussed.

An attempt is made to differentiate the picture of acute myocardial infarc-

tion with predominantly central nervous system symptoms from the combined acute vascular lesions of the brain and heart.

The use of the electrocardiogram, electroencephalogram, and improved pathologic techniques to aid in that differentiation are discussed.

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THE EFFECT OF CORTISONE IN EXPERIMENTAL MYOCARDIAL INFARCTION*

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The effect of acute myocardial infarction in lowering blood pressure is well known[7]. That shock definitely adds to the gravity of the prognosis in this condition is appreciated as well[6,7,10]. For some time it has been observed that adrenal cortical extract has been of benefit in cases of shock, especially those associated with adrenal cortical insufficiency[2,4,11]. With this knowledge it was thought that cortisone might aid in combatting shock due to myocardial infarction. Several reports in the literature have stressed the effect of cortisone on mesenchymal tissue and adverse effects on healing[1]. Prior to instituting cortisone therapy in humans, it was decided to investigate its effects on the electrolyte balance, adrenal glands, and heart in acute and chronic myocardial infarction produced experimentally in dogs.

Method and Material. Groups of mongrel dogs, weighing between 18 and 35 lbs. and having a myocardial infarction produced by ligation of the left anterior descending coronary artery, were treated with cortisone for 10-day periods of time. At the end of 10 or 30 days after initiation of therapy, the dogs were sacrificed and autopsies were performed. Included in the study were daily eosinophil counts, sodium and potassium determinations, serial electrocardiograms, and gross and microscopic examinations of the heart, lungs, and adrenal glands. There were 6 treated and 6 untreated control animals in each group. At the beginning of the study, cortisone was used in the dosage of 3 mg. per Kg., but later in the study the dosage was changed to 7 mg. per Kg. From eosinophil counts it would appear that the latter dosage is the more satisfactory one.

Under sodium pentobarbital anesthesia, administered intravenously in a dosage of 30 mg. per Kg., the left chest of the dog was entered. Respirations were continued by the use of either tracheotomy or endotracheal tube with a mechanical respirator at the rate of 18 per minute. The left anterior descending coronary artery was tied off either by placing a ligature around the artery and vein and through the myocardium and tying immediately, or by isolating the artery from the vein as described by Harris[3]. In each set of experiments the treated and control dogs were operated upon similarly. The coronary artery was tied off just distal to the tip of the left auricular appendage.

The eosinophil counts were done by a modification of the Thorn method. The diluting solution was made up as follows:

2% yellowish eosin, aqueous	0.2 cc.
Acetone	0.5 cc.
Distilled water	9.0 cc.

This solution was refrigerated when not in use and was freshly prepared

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each week. Otherwise, the counts were done as described by Roche, Thorn and Hills[9]. Sodium and potassium concentrations were ascertained using a Beckman flame photometer[8]. Electrocardiograms were taken before and after operation, 3 times weekly for 10 days, and then every 5 days until the dogs were necropsied.

Results. 1) Eosinophil Counts. In control untreated dogs, the eosinophil count dropped to 50% or less the day following infarction, with a rise to levels higher than normal (150 to 200) between the second to the fifth postoperative day, followed by a leveling off to preoperative values. About 3 weeks after infarction control dogs developed a secondary rise in the eosinophil count to higher levels, that is, to more than 300% of the preoperative level.

The eosinophil count in treated dogs was similar to that in controls receiving cortisone in doses of 3 mg. per Kg. of body weight. In those dogs which received cortisone in doses of 7 mg. per Kg., the eosinophil count fell during treatment to quite low levels (less than 10%); these values were persistent for 10 to 14 days after cessation of treatment. After 3 weeks the eosinophil count in treated dogs became much higher than the preoperative level (Fig. 1).

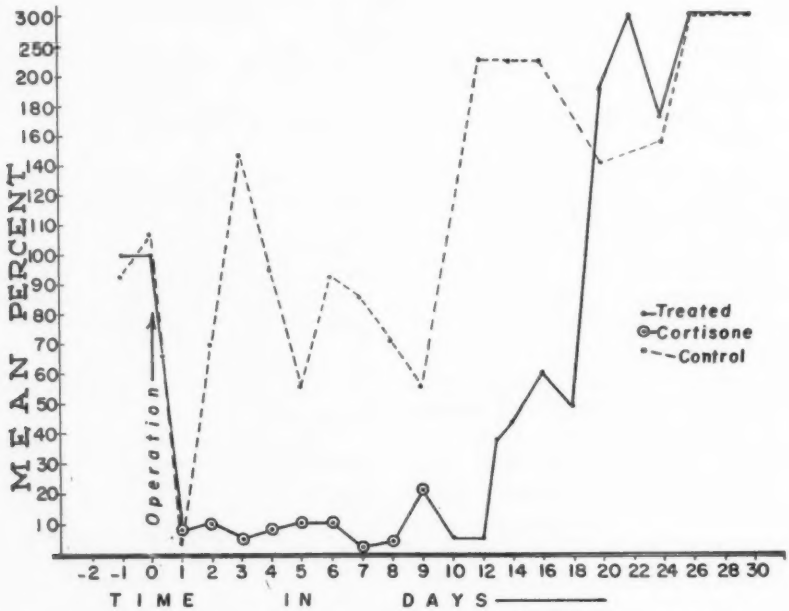

Fig. 1.—Graphic illustration of the eosinophil count expressed in mean % of preoperative count in control and cortisone-treated animals.

2) Sodium and Potassium. There was no evidence of any significant electrolyte disturbance in the blood when the control group was compared with the treated group.

3) Electrocardiogram. The most consistent electrocardiographic finding was the development of premature ventricular beats with runs of ventricular tachycardia. Depression of ST segments occurred frequently postoperatively. Q waves and inverted and cove plane T waves frequently ap-

peared in the first 2 postoperative days. The T waves became upright again between the 4th and 6th postoperative days. After the 6th day the only abnormalities were upright coronary T waves as described by Katz[5].

4) Pathological Observations. Control and treated groups were compared as to gross and microscopic findings in the adrenal glands and in the infarcted areas of the myocardium. No significant changes were noted in the gross appearance and/or weight of the adrenal gland. Vacuolation of the adrenal cells, both medullary and cortical, was slightly more prominent in the group treated for 10 days. At 30 days, there was no significant difference microscopically in the adrenal glands of the control or treated groups of dogs.

No significant gross differences were noted in the areas of myocardial infarction of the 10-day and 30-day groups when these were compared with the corresponding areas in the controls. There was slightly less coagulative necrosis in the 30-day treated animals than in the controls. Bluish staining areas compatible with areas of calcification were seen much more frequently in the treated animals, both in the 10-day and 30-day groups, than in the controls. No significant difference was noted in inflammatory response, as indicated by the presence of leukocytes in the infarction, or in the degree of fibrosis present, in the control or in the cortisone-treated 10-day or 30-day groups.

Discussion. The previously reported effects of cortisone in experimental animals have shown an atrophy of the adrenal glands as reflected in 40 to 60% reduction in weight of the glands and cytological changes with thinning of the reticular and fascicular zones[13]. Studies in animals and humans have revealed a variable degree of electrolyte disturbance and secondary hormonal changes. It has been recommended that cortisone therapy be avoided in cardiac decompensation because of the sodium retention which accompanies therapy with this steroid. From certain theoretical standpoints, especially that of possible retardation of healing, cortisone would seem to be contraindicated in myocardial infarction. However, in this group of studies it was not possible to recognize any deleterious effects of cortisone therapy in the gross size or histological appearance of myocardial infarctions in the dog.

That sufficient cortisone was being administered to cause a definite effect was reflected in the lowering of the eosinophil count to levels which have been found to be consistent with adequate therapy[12]. In our early studies it was found that cortisone in doses of 3 mg. per Kg. did not evoke the degree of lowering of the eosinophils that has become accepted as necessary for evidence of sufficient dosage. The 7 mg. per Kg. dose did bring about this response. The failure of cortisone to cause significant electrolyte disturbance at this dosage level lends support to the belief that cortisone might be used with caution in acute myocardial infarction in humans.

There was definite but not marked histological evidence of atrophy of the adrenal glands after 10 days of cortisone therapy. No significant changes in the adrenal glands of the treated dogs in the 30-day group were noted. This may reflect the rapid return to normal of the adrenal gland following cessation of treatment as noted by Winter *et al.*[13].

Summary. Cortisone given in therapeutic amounts to dogs with experimentally produced myocardial infarction produced no deleterious effect on the size of the infarction or on the rate or quality of myocardial healing. There was slight evidence of adrenal cortical

atrophy after 10 days of treatment with cortisone, but 20 days after cortisone was discontinued the adrenals were normal. No significant electrolyte disturbance resulted from cortisone therapy in these experiments.

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THE RESPONSE OF PATIENTS WITH CONGESTIVE HEART FAILURE TO A RAPID ELEVATION IN ATMOSPHERIC TEMPERATURE AND HUMIDITY*

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Previous investigations concerning effects of climate and experimentally controlled atmospheric conditions have dealt chiefly with normal man. There is evidence that persons with cardiac disease die readily from heat stroke, especially during heat waves in the nontropical areas of the world[12]. In general, persons with impairment of circulation tolerate a hot environment relatively poorly, particularly when the changes occur suddenly; for example, the hot environment in the Kettering hypertherm during fever therapy has produced episodes of pulmonary edema[11]. Acute cardiac asthma has also been precipitated in patients with congestive heart failure by a hot and humid environment[6,7]. The present investigation is concerned with the study of certain physiologic reactions of subjects with chronic congestive heart failure and of control subjects without cardiac disease upon exposure to a hot and humid environment.

Method. Twenty-five subjects (13 controls and 12 with varying stages and degrees of chronic congestive heart failure) were studied. The clinical data are summarized in Table 1. Subjects 11, 16, 21, and 23 had no previous therapy. All subjects were permitted to rest on a comfortable hospital bed for 60 to 90 minutes, clothed in a cotton gown, in the controlled observation room before the environment was made hot and humid. During this time basal clinical data were obtained: cardiac and respiratory activity, blood pressure (sphygmomanometrically determined), color of skin, sweating, general clinical appearance and psychic reaction. The laboratory atmosphere was then changed from 23° (± 1°) C. and 60% (± 10%) relative humidity to 40° (±2°) C. and 85% (± 15%) relative humidity in less than 15 minutes, a temperature of 38° C. being reached in 3.5 minutes, the remainder of the time being required for final stabilization of the atmosphere. Air velocity was below 15 ft./min. The subjects remained in the hot and humid environment for 40 to 114 minutes, the duration of exposure being governed by the tolerance of the subject. The observations were then continued for 1 to 2 hours until the subjects approached or returned to the "basal" state. In 3 experiments, a control subject and one with congestive heart failure were observed simultaneously in the same air-conditioned room.

Rectal and skin (calf) temperatures were recorded by means of thermocouples. Body weight was determined on a clinical balance (accuracy of ± 50 gm.) before and at the end of each experiment.

Results. Results are summarized in detail in Table 1. Ten of the 12 subjects with mild congestive heart failure reacted severely to the hot and humid room atmosphere by presenting the symptoms and signs of the syndrome of left ventricular congestive heart failure, necessitating immediate return of the atmosphere to comfortable conditions to avoid serious consequences. In 5 of them the failure was extreme.

* Aided by grants from the Life Insurance Medical Research Fund, a War Department Grant No. W-49-007-MD-389, and the Mrs. E. J. Caire Fund for Research in Heart Disease.

TABLE 1.–PERTINENT CLINICAL AND EXPERIMENTAL DATA

A. CONTROL SUBJECTS

Subject No.	*Color, Sex, Age*	*Mo. of Study*	*New Orleans T. & RH**	*Diagnosis*	*Exposure time (min.)*	*Wt. loss during study (Kg.)*	*Degree and Manifestations of Reactions to Environment†*
1	C M 50	Sept.	74–83° 68–88%	Normal	110	1.25	*Mild* to *moderate.* Tolerance excellent; hyperventilation, weakness, irritability, and anxiety
2	W F 42	Sept.	74–83° 68–88%	Psychoneurosis	64	0.46	*Moderate.* Intolerance; hyperventilation, extreme anxiety, irritability, hysteria
3	C M 47	Sept.	74–83° 68–88%	Mild dyspepsia	114	2.04	*Mild* to *moderate.* Tolerance excellent; limit not reached
4	C F 41	Sept.	74–83° 68–88%	Inguinal hernia	87	0.80	*Mild* to *moderate.* Tolerance good; tachycardia, decreased pulse pressure with faintness, rapid recovery
5	W M 35	Oct.	74–83° 68–88%	Serum sickness, convalescent, mild bronchial asthma	71	1.19	*Moderate.* Tolerance good; chiefly CNS reaction-irritability, anxiety, muttering, incoherent speech
6	C F 30	Oct.	69.5–83.3° 70–93%	Penicillin reaction, convalescent	63	0.46	*Moderate.* Tolerance good; hyperventilation syndrome, apical systolic and aortic diastolic murmurs developed
7	W M 25	Nov.	53.1–70.8° 45–76%	Myalgia, bronchial asthma	56	0.57	*Severe.* Decreased tolerance; precipitated bronchial asthma, wheezing, forced expiration, râles
8	W M 33	Dec.	51.6–66.3° 72–87%	Infectious hepatitis, convalescent	84	1.92	*Mild* to *moderate.* Tolerance good; tachypnea
9	C M 45	Dec.	51.6–66.3° 72–87%	Minimal bronchiectasis	89	1.37	*Mild* to *moderate.* Tolerance good; slight hyperventilation, mild respiratory alkalosis
10	C M 33	Dec.	51.6–66.3° 72–87%	Inguinal hernia	69	1.02	*Mild* to *moderate.* Tolerance good; weakness, anxiety, restlessness

B. SUBJECTS WITH CONGESTIVE HEART FAILURE

11	W M 34	Jan.	54–64° 70–89%	Cor pulmonale, mild, slight cardiomegaly, bronchiectasis, I**	50		*Severe.* Dyspnea, extreme tachycardia, gallop
12	W F 48	March	56–65° 76–91%	Rheumatic mitral stenosis, moderate cardiomegaly, auricular fibrillation, II	94		*Severe.* Weakness, dyspnea, and irregular, labored respiration
13	W F 51	March	56–65° 76–91%	Hypertension, marked cardiomegaly, pulsus alternans, II	87	2.04	*Moderate.* Dyspnea, faintness, heaviness over precordium, and multiple minute hemorrhages over forearm, gallop
14	C M 60	March	57–67° 61–87%	Syphilitic aortic insufficiency, moderate cardiomegaly, II	97	0.91	*Severe.* Weakness, irritability, ventricular premature beats increased, dyspnea and râles
15	C M 55	May	72–84° 62–87%	Hypertension, moderate cardiomegaly, gallop, cardiac cirrhosis, II	73	1.59	*Moderate.* Increased intensity of gallop, irritability, weakness, urinary incontinence
15	Same	Sept.	77–89° 63–89%	Hypertension, marked cardiomegaly, gallop, pulsus alternans, III	84	1.19	*Severe.* Gallop intensified, weakness, dyspnea, recovery slow
16	W F 32	May	72–84° 62–87%	Rheumatic mitral stenosis, hypertension, marked cardiomegaly, gallop, pulsus alternans, III	43	0.80	*Severe.*‡ Chiefly respiratory distress, extreme dyspnea, râles, gallop intensified
17	C M 53	May	72–84° 62–87%	Syphilitic aortic insufficiency, slight cardiomegaly, I	103	2.27	*Mild* to *moderate.* Tolerance good; hyperventilation
18	C M 37	Sept.	74–83° 68–88%	Rheumatic mitral stenosis, moderate cardiomegaly, II	69	0.46	*Severe.* Extremely dyspneic, coughing, respiratory hyperventilation syndrome, appearance of premature beats

TABLE 1.—PERTINENT CLINICAL AND EXPERIMENTAL DATA—(*Continued*)

Subject No.	*Color, Sex, Age*	*Mo. of Study*	*New Orleans T. & RH**	*Diagnosis*	*Exposure time (min.)*	*Wt. loss during study (Kg.)*	*Degree and Manifestations of Reactions to Environment†*
19	C M 48	Sept.	74–83° 68–88%	Hypertension, moderate cardiomegaly, gallop, C-S. respiration, III	55	1.48	*Severe.*‡ Extreme dyspnea, gallop intensified
				C. SUBJECTS STUDIED SIMULTANEOUSLY			
20	C F 38	Oct.	69.5–82.3° 70–93%	Control, obesity	56	0.34	*Mild.* Response minimal
21	C F 44	Oct.		Hypertension, moderate cardiomegaly, gallop, II		0.46	*Severe.*‡ Severe dyspnea, râles, appearance of gallop, orthopnea
22	C F 58	Oct.	69.5–82.3° 70–93%	Control, mild diabetes mellitus	40	0.23	*Mild.* Response minimal
23	C F 49	Oct.		Hypertension, moderate cardiomegaly, gallop, III		0.23	*Severe.*‡ Dyspnea extreme, gallop intensified, râles
24	C F 56	Oct.	69.5–82.3° 70–93%	Control, hypertension, obesity	71	0.68	*Mild.* Slight elevation of pulse rate
25	C F 53	Oct		Hypertension, arteriosclerosis, slight cardiomegaly, I		1.19	*Severe.*‡ Dyspnea, gallop, orthopnea

* Range during month prior to study, obtained from U. S. Weather Bureau
† Gradation of reaction
a) mild-minimal: discomfort, sweating
b) mild to moderate: tachycardia, irritability, tachypnea
c) moderate: hyperventilation, restlessness, faintness
d) severe: respiratory distress, râles, gallop rhythm, orthopnea, apprehension
** New York Heart Association Functional Classification.
‡ Precipitated "acute left ventricular failure:" cardiac asthma, extreme dyspnea, pulmonary râles, gallop rhythm, anxiety.
Subject No. 15 was observed on two occasions 4 months apart. At the time of the last study the state of the congestive heart failure was worse. Subjects No. 11, 16, 21, 23, were not digitalized at the time of the study.

The control subjects with diseases other than congestive heart failure tolerated the hot and humid environment as well as did normal subjects.

In general, however, tolerance to heat varied considerably for all subjects. The more significant symptoms and signs produced for all subjects are summarized in Table 2. The general physiologic pattern of response to the hot and humid atmosphere was more uniform in the control subjects than in those with cardiac disease and chronic congestive heart failure. The clinical reaction of normal individuals to similar environmental stress has been described previously by others[1-3,5,16] and is well illustrated by Fig. 1 for a typical control subject (No. 3). The values plotted represent percentage changes from the basal values. Initially there was a rise in skin temperature, followed shortly by a more gradual rise in rectal temperature. Tachycardia developed, respiratory activity increased, tachypnea, hyperventilation, and slight dyspnea occurred, and in some the hyperventilation syndrome appeared. Extreme peripheral vasodilatation developed in association with a great increase in pulse pressure. Blanching and wrinkling of the skin of the extremities appeared after prolonged exposure. The systolic blood pressure remained essentially unchanged, occasionally decreasing during the early period of exposure or rising terminally in some subjects. The diastolic component decreased considerably and, as recorded by the fifth phase of the Korotkow sounds, fell to zero. As the exposure continued, the subjects became irritable, complained of weakness, faintness, and of being extremely hot. Further exposure produced evidence of involvement of the central

TABLE 2.–SIGNS AND SYMPTOMS OF THEORETIC IMPORTANCE WHICH DEVELOPED UNDER THE INFLUENCE OF THE HOT AND HUMID ATMOSPHERE

A. Cardiovascular System

1. Increased cardiac activity
   a. Increase in cardiac rate
   b. Development or intensification of murmurs
2. Blood pressure changes
   a. Systolic–increase or decrease
   b. Diastolic–decrease
3. Gallop rhythm–development or intensification
4. Pulsus paradoxus
5. Pulsus alternans
6. Cardiac arrhythmias
7. Syncope (faintness)
8. Venous engorgement
9. Hemorrhagic phenomenon
10. Blanching and wrinkling of skin of extremities at end of exposure

B. Respiratory System

1. Increased respiratory activity
   a. Hyperventilation and hyperventilation syndrome
   b. Dyspnea and orthopnea
   c. Coughing
2. Râles
3. Cardiac and allergic type asthma

C. Central Nervous System

1. Irritability and restlessness
2. Weakness and anxiety
3. Headache
4. Visual disturbances
5. Bladder incontinence
6. More advanced nervous disorders

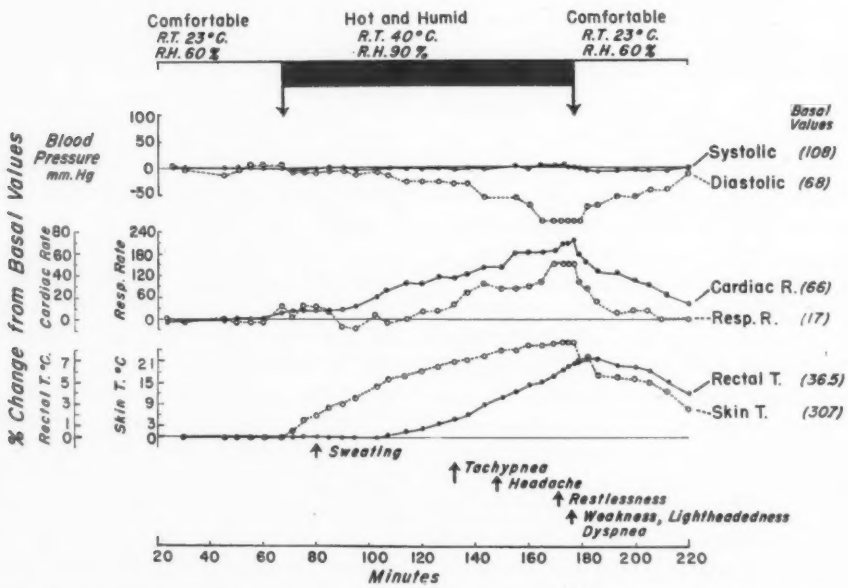

Fig. 1.–Summary of certain physiologic data obtained on control Subject 3. It can be observed that the cardiovascular and pulmonary systems began to change after approximately 40 minutes of exposure to the hot and humid atmosphere. As the duration of exposure to the environment progressed, the symptoms and signs of physiologic disturbances became intensified. Consult text for other details.

nervous system, such as headaches, visual disturbances, restlessness, and muscular tremors. The exposure was not continued beyond such a point in order that the serious manifestations might be avoided[1,9,10,13,15,17]. In none of the control subjects was gallop rhythm, pulmonary congestion, or evidence of left ventricular failure observed, although the durations of exposure were carried essentially to the subjects' voluntary limits.

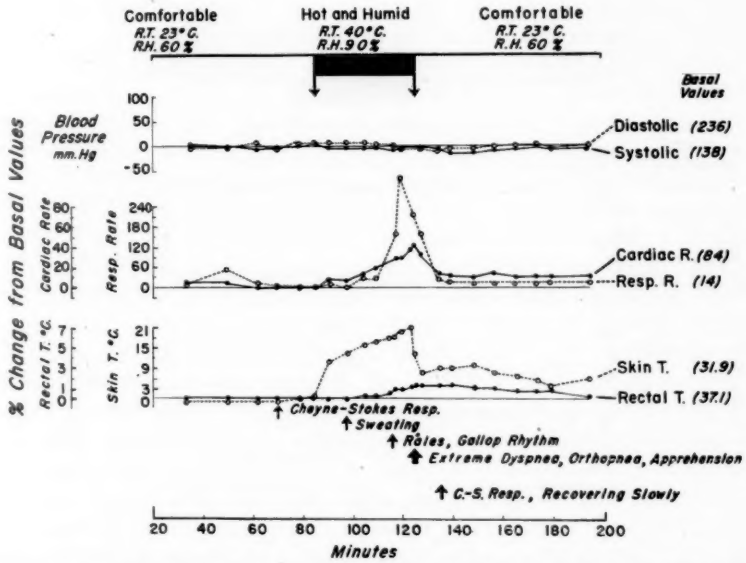

FIG. 2.—Summary of certain physiologic data obtained on Subject 23 with chronic congestive heart failure and hypertensive cardiovascular disease. The subject was without medication for 2 weeks prior to the experiment. Under the influences of the hot and humid atmosphere, clinical manifestations of acute cardiac asthma developed, being characterized by extreme dyspnea and orthopnea, diffuse râles in the lungs and intensification of gallop rhythm. It was necessary to change the atmospheric conditions rapidly in order to prevent serious consequences. Consult text for other details.

The reaction manifested by the subjects with chronic congestive heart failure was basically similar to, but less predictable than, that for the control subjects. Important differences were noted. Duration of exposure to the hot and humid atmosphere was usually less for the subjects with congestive heart failure than for the control subjects because of the former's exaggerated intolerance to this environment. Dyspnea was the most prominent symptom. When a subject with congestive failure and a control subject were observed side by side, in the same atmospheric surroundings, the former developed extreme dyspnea, orthopnea, apprehension, and other evidences of "left ventricular" failure at a time when the control subject without cardiac disease just began to sweat and exhibit an increased cardiac rate (Figs. 2 and 3). In the subject with chronic congestive heart failure the appearance of pulmonary râles, dyspnea, venous engorgement, and gallop rhythm usually indicated the onset of acute cardiac asthma. Gallop rhythm was accentuated or produced in 9 of the patients with chronic congestive heart

failure. The state of decompensation, stage of the heart failure, and previous therapy seem to have had an influence on their responses to the hot and humid atmosphere.

Certain other specific physiologic details deserve mention. Murmurs were produced or intensified in both groups but greater cardiac stress, as manifested by a bounding precordium and epigastric pulsations, was noted in the environment in general was less than for the controls. Cheyne-Stokes respiration disappeared when dyspnea was precipitated by the hot and humid atmosphere and reappeared during the recovery period. In general, the onset of the rise in body temperature occurred later in the control subjects, whereas the hyperthermia was more sustained in the patients with congestive heart failure after return to a

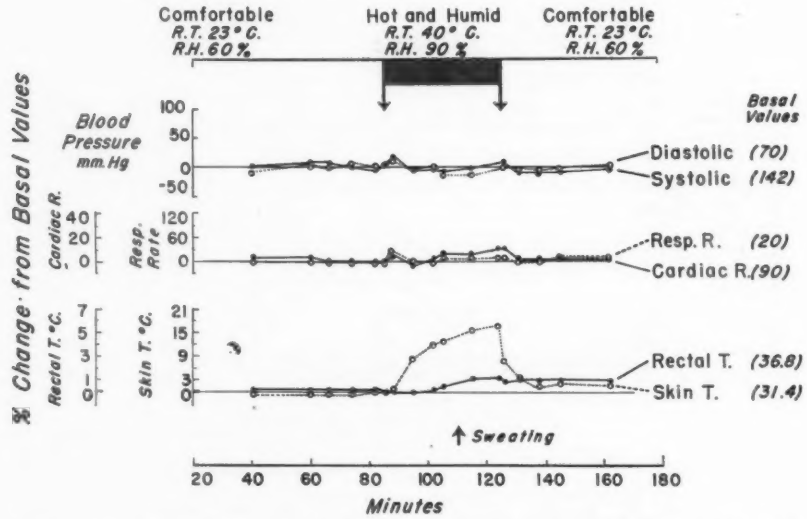

FIG. 3.—Summary of certain physiologic data obtained on control Subject 22 without any clinical evidence of cardiac disease. She was observed simultaneously with Subject 23, whose data are presented in Fig. 2. Their respective reactions may be compared by a study of Figs. 2 and 3. These data may also be compared with those obtained during the early period of observation of control Subject 3 (Fig. 1). The physiologic responses presented in Figs. 1 and 3 probably differ because the duration of exposure of the 2 subjects to the hot and humid environments varied.

subjects with cardiac disease. The only cardiac arrhythmias that developed during these experiments were premature contractions. The premature beats, if present already, usually became less frequent with appearance of the tachycardia and recurred when the cardiac rate fell during recovery from the heat. The diastolic pressure tended to decline less in the subjects with heart failure, although the duration of exposure to the hot and humid comfortable environment. The subjects with chronic congestive heart failure lost more weight in the hot and humid room than did the controls who were being studied at the same time. The mean weight loss for the subjects with chronic congestive heart failure and the control subjects observed simultaneously was 0.43 Kg./hr./m^2 and 0.24 Kg./hr./m^2, respectively.

The return to the physiologic state observed for the comfortable atmos-

phere was less rapid in the patients with congestive heart failure, as judged by the rapidity of the decrease in cardiac rate, subsidence of dyspnea, and state of well-being. In most instances all subjects returned to their respective previous basal states within an hour or two.

The subjects with chronic pulmonary diseases likewise tolerated the hot and humid atmosphere with difficulty. For example, Subject 7 with intrinsic bronchial asthma developed asthmatic wheezes and pulmonary râles with labored respiration.

Discussion. Subjects with advanced arteriosclerosis, history of myocardial infarction, severe congestive heart failure, or uremia were excluded from these studies to avoid serious irreversible complications. The subjects selected with mild failure had been observed for several days in the hospital during therapy and compensation was established before they were studied. Extreme caution and close observation in the laboratory were constantly maintained to avoid serious reactions.

In order to interpret the effects of climatic surroundings on an individual, healthy or otherwise, one must consider the characteristics of the atmosphere and duration of exposure. A study of such short duration with acute exposure to a hot and humid atmosphere made it impossible for phenomena of acclimatization to develop and influence the responses. Fortunately, the changes in climate encountered in nature are usually slow, so as to allow some physiologic adaptation by subjects with both a normal and an abnormal cardiovascular system. Furthermore, the levels of both temperature and humidity of the atmosphere are not so high in inhabited areas of the world. When there is a sudden, extreme elevation in environmental temperature, the populace of the area suffers considerably, especially those with cardiovascular diseases.

Among the organic systems which become taxed when man finds himself in a hot and humid environment is the cardiovascular system. In these experiments acute left ventricular congestive heart failure was probably precipitated in the subjects with preexisting mild failure because of the increased activity produced. It is well known that whenever man finds himself in a hot and humid environment in which the elimination of body heat is impaired or impossible, there follows vasodilatation of the vessels of the skin with increased cardiac rate, more rapid circulation, and increased cardiac output per minute. This is probably associated with an increase in cardiac work. In the presence of cardiac disease with impairment of cardiac reserve, a clinical syndrome of acute left ventricular failure might be expected to develop. The additional burden on thermo-regulation and the added load on the cardiovascular system may be analogous to a form of strenuous exercise. Because the subjects with congestive heart failure were not able to tolerate the exposures as long as were the control subjects, less pronounced changes of blood pressure and evidence of strain on the central nervous system occurred.

These and previous experiments suggest possible advantages in the use of a hot and humid environment in applying "stress" upon the cardiovascular system for experimental purposes in the study of physiologic phenomena concerned with congestive heart failure. By this method it is possible to precipitate the clinical syndrome of failure without moving the subject. thus permitting various studies to be made before and after failure. Failure precipitated by this method may be compared to that induced by the

"stress" of exercise, which, however, requires the subject to move.

It is not possible to state the mechanisms by which congestive heart failure is precipitated by this type of stress. The problem of the mechanism of congestive heart failure is an extremely complex one. Consideration of the problem and its possible relationship to the hot and humid environment have been presented elsewhere[8].

Although many of these observations were not of a precise nature, they did indicate certain interesting details, common to both types of subjects studied, which need further investigation. As stated previously, many of these subjects developed hyperventilation and dyspnea, but the basis for these reactions to heat is not definitely known. Dogs and other animals employ panting as a means of heat dissipation, and it has been shown that man eliminates heat by convection and volatilization of water from the respiratory system[6]. The increased respiratory rate of ventilation must be due in part to the demands for intake of O_2 and excretion of CO_2 associated with the increase in metabolism produced by the hot and humid environment. The rapid respiratory rate subsides dramatically, following closely the fall in temperatures of the skin and upper respiratory mucosa in response to cooling, despite the fact that rectal temperature may remain increased several degrees or may even continue to rise. This suggests reflex control through the central nervous system. In some of these individuals in our experiments, toward the end of the period of exposure to heat, peripheral blanching developed, which may have been related to the hyperventilation[4] or may have represented compensatory peripheral vasoconstriction.

It is a common observation in cardiac clinics or on the wards of hospitals located in subtropical areas that during the summer months patients with chronic congestive heart failure labor under the additional strain of the heat, especially if they exert themselves. They complain of their intolerance to the climate and note exaggerated dyspnea and a sensation of suffocation. In the large cities of nontropical areas, persons with congestive heart failure and the aged are particularly subject to heat stroke during sudden changes of the weather and recurrent heat waves. Although the present studies, which are acute experiments, do not precisely simulate natural climatic conditions, they nevertheless indicate that patients with congestive heart failure are intolerant of excessive environmental heat. Statistically, the winter months are associated with higher death rates for patients with congestive failure, but the problem of death rates, which must take into account infections, is complex[14].

The present experiments indicate the value of maintaining a comfortable environmental atmosphere for the patient with cardiac disease and suggest that more attention be given to the environmental conditions during therapy. Greater use of air conditioning of wards or hospitals for the patient with cardiac disease would probably be desirable.

Summary. Patients with congestive heart failure were observed under the influence of sudden elevation of environmental atmospheric temperature and relative humidity and their reactions were compared with those of individuals without cardiac disease. The hot and humid surroundings precipitated acute attacks of left ventricular failure (cardiac asthma), characterized by severe dyspnea, râles, and gallop rhythm, associated with apprehension and panic. The subjects with advanced cardiac disease were less able to combat the stress of environ-

mental heat than were the subjects without cardiac disease. Indications seem to exist for greater use of air conditioning of hospital wards and rooms of cardiac patients. Since the stress of a hot and humid environment is not conducive to physical or mental rest, patients with cardiac disease should benefit considerably by living in a comfortable atmosphere.

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LEUKEMOID BONE MARROW IN PERNICIOUS ANEMIA*

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THE morphology of the bone marrow during relapse in pernicious anemia is considered pathognomonic of the disease. The characteristic megaloblastic arrest, studied extensively by Zadek[6] and Peabody[5] a quarter of a century ago, has become so well recognized that few would consider the diagnosis of pernicious anemia in relapse in its absence. That complicating disorders may profoundly alter this histologic picture has not been appreciated.

It is the purpose of this communication to report the cases of 2 patients with Addisonian pernicious anemia in relapse in whom bone marrow specimens showed intense myelocytic activity with insignificant numbers of megaloblasts and in whom the diagnosis of leukemia was seriously entertained by the attending physician.

Case Reports. CASE 1. A 35-year old physician was admitted to the Minneapolis Veterans Administration Hospital on July 14, 1950, complaining of fever, headache, and malaise.

Four days before entry he noted severe abdominal bloating and discomfort associated with constipation. Two days before entry he arose in the morning feeling somewhat feverish and, several hours later, experienced a severe shaking chill. In the afternoon of the same day his temperature rose to a maximum of 104° F. In the evening severe malaise and retro-orbital headache set in. The day before entry there were several bouts of diarrhea and abdominal cramps but no blood was seen in the stools. When the symptoms failed to clear on the fourth day of the illness, he sought hospitalization.

Inquiry into the past history disclosed that the patient had suffered numerous attacks of diarrhea during wartime service in Egypt, China, and Indo-China. On several occasions the stools contained gross blood and in 1945 a presumptive diagnosis of amebiasis was made. Since there was some doubt as to the presence of *E. histolytica* in the stools, and since the symptoms cleared spontaneously, no specific treatment was given. Proctoscopy and barium enema at the time failed to disclose anything abnormal. From 1946 to 1950, he often complained of loose stools and mild abdominal cramps, but repeated studies of the stools were negative. Over the same period he noted occasional bouts of epigastric pain, usually coming on several hours after meals and always relieved by food or antacids. He recalled having experienced the same complaint in 1943 at which time gastrointestinal Roentgen-ray examination was negative. A second examination in 1948 was also negative. In the year previous to hospitalization, there were several attacks of glossitis and

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration

stomatitis during which the tongue became fiery red and denuded of papillae; during one of the attacks, the appearance of the tongue was observed by a colleague but the episode was dismissed at the time since it lasted only a few days. In 1948, because of daily exposure to Roentgen-rays, several routine hemoglobin estimations were carried out; the results ranged from 12.0 to 12.4 gm., and because of these values, the patient temporarily stopped working with Roentgen-ray techniques.

The family and social histories were noncontributory.

Physical examination disclosed an acutely ill, drowsy man whose conjunctivae were moderately injected. The temperature was 103.2° F. There was a moderate amount of gray hair. The neck was not stiff and the optic discs and fundi were normal. The pharynx was slightly injected. The chest was clear and examination of the heart was normal except for a moderate tachycardia. The blood pressure was 130 mm. Hg. systolic and 56 diastolic. The liver was palpable 3 fingerbreadths below the right costal margin. The spleen was easily palpable but was not tender. Nothing abnormal was found on examination of the genitalia, rectum, and extremities. The deep tendon reflexes were normal. There were no skin lesions or significant lymphadenopathy.

The red blood cells were 2.8 million per cu. mm., the hemoglobin 10.8 gm. per 100 cc., the hematocrit 32%, and the white blood cells 4,600 per cu. mm., with 68% polynuclear neutrophils, most of which were band forms, 17% lymphocytes, and 15% eosinophils. The mean corpuscular volume was 114 cu. microns. There was moderate variation in size and shape of the erythrocytes with a number of macrocytes. Both the neutrophils and the lymphocytes showed marked toxic granulation. The platelets numbered 76,000 per cu. mm.

Urinalysis was normal. Three purged stool specimens were negative for parasites and occult blood. Agglutinations for *Brucella* and *P. tularensis* were negative. Agglutination for typhoid and paratyphoid organisms was not significantly elevated. The Weil-Felix reaction was negative. Heterophil antibody was absent at first and present in insignificant titer later. Blood Kahn and Wasserman tests were negative. Stool cultures showed no pathogenic organisms and blood cultures were negative. A complete series of liver function studies yielded results that were within the normal range. Gastric analysis showed 10° of total and no free acid before and after histamine. Roentgenograms of the chest were negative.

The patient was treated symptomatically at first. The temperature slowly returned to normal during the first 4 days of the hospital stay but abdominal bloating and alternate bouts of constipation and diarrhea persisted. During this period the leukocyte count and the hemoglobin declined, the lowest values being 1,850 and 9.8 gm., respectively. Concurrently the neutrophils declined to 26% (Table 1). Some of the neutrophils were hypersegmented but most were immature late metamyelocytic

TABLE 1.—BLOOD FINDINGS IN CASE 1

						Differential Leukocyte Counts: Percentages						
						Neutrophils						
Date	*RBC millions/ cu.mm.*	*Hbn.† gm./ 100 cc.*	*Hct.‡ %*	*Reticulocytes %*	*WBC thousands/ cu.mm.*	*Segmented*	*Band Forms*	*Eosinophils*	*Basophils*	*Lymphocytes*	*Monocytes*	*Platelets thousands/ cu.mm.*
7/13		11.6	31		3.4	66	15	8	0	8	3	
7/15	2.8	10.8	32	0.1	4.6							76.0
7/18	2.3	10.2		0.2	2.7	19	5	7	1	66	2	92.7
7/19	2.7	10.4	32	0.1	1.8	22	23	4	5	43	3	101.7
7/20		9.8		0.1	2.7							
7/21		10.5		0.6	6.4	28	21	1	4	44	2	
7/22		10.7		4.4	5.8							
7/23		11.5		8.0	6.0	40	15	0	4	39	2	
7/24	2.9	10.4	35	12.7	5.1							
7/25		11.0		12.9	5.1	41	18	2	4	34	1	
7/26		11.4	36	9.5	5.3							120.0
7/27		11.0		9.5								
7/28		11.5		7.1								
7/29		11.8		4.6								
8/24	3.7	13.7	42.5	1.6	9.4		84*	1	1	12	2	
12/7	5.4	14.1	45	1.4	9.4		74*	1	0	22	3	

* No differentiation was made between adult polymorphonuclear and band form neutrophils on these 2 films
† Hemoglobin
‡ Hematocrit

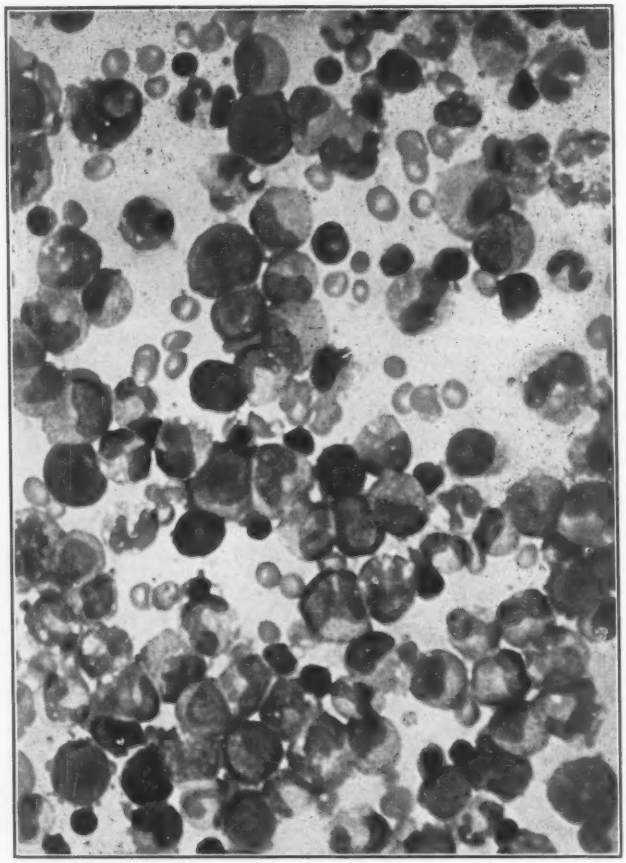

FIG. 1.—Bone marrow film in Case 1.

forms. No blast cells were seen. A bone marrow aspiration (Fig. 1) done on July 18 showed 86% of the cells to be of the granulocytic series (Table 2), mostly neutrophilic myelocytes and metamyelocytes. Development appeared arrested at the latter stage. Increased numbers of eosinophils and basophils with prominence of immature forms were noted. The number of cells of the erythroid series that could be classed as megaloblasts were few in number and could with difficulty be distinguished from erythroblasts.

The clinical findings, together with the appearance of the peripheral blood and bone marrow, led most observers to favor the diagnosis of atypical leukemia. It should be noted, however, that the true significance of the gastrointestinal symptoms was appreciated by neither the patient nor the attending physicians; as a matter of fact, the presence of

TABLE 2.—RELATIVE NUMBERS OF NUCLEATED CELLS IN ASPIRATED BONE MARROW SAMPLES (1000 CELLS COUNTED)

	Case 1. %	*Case 2.* %
Myeloblasts	11.4	4.0
Promyelocytes	7.0	13.4
Myelocytes:		
Neutrophilic	18.2	23.3
Eosinophilic	4.2	5.2
Basophilic	0.6	1.0
Metamyelocytes (and bands)	42.2	18.8
Polymorphonuclear neutrophils	2.3	3.2
Lymphocytes	7.0	6.1
Plasma cells	0.5	0.7
Monocytes	0.0	0.3
Megakaryocytes	0.3	0.6
Megaloblasts	0.7	3.0
Erythroblasts	2.8	14.6
Normoblasts	2.8	5.8

glossitis and stomatitis was recalled by the patient only after the correct diagnosis had been made. After the initial examination of the bone marrow, it was decided to institute treatment with vitamin B_{12}, although there was little expectation that it would influence the course of the disease. An initial dose of 45 mcg. was given intramuscularly on the evening of July 18 and subsequently the daily dose was 15 mcg. Changes in the peripheral blood before and after this date are shown in Table 1. It will be noted that on July 21, 4 days after treatment with vitamin B_{12} was begun, the leukocyte count rose from 2,750 to 6,400, although the neutropenia persisted. On July 22, the reticulocyte count rose to 4.4% and reached 12.9% on July 25. Within 48 hours after the first dose of vitamin B_{12} was given, there was pronounced improvement in the gastrointestinal symptoms. Anorexia, which had been severe during and immediately after the febrile period, gave way to an almost ravenous appetite. Abdominal discomfort disappeared entirely and bowel movements became normal. The spleen receded rapidly. At discharge, on July 28, the patient was entirely asymptomatic.

The patient returned to full activity almost immediately, and has been maintained on 15 mcg. of vitamin B_{12} every 2 weeks. There has been no recurrence of the fever or gastrointestinal symptoms. Three months after the onset of the acute episode the bone marrow was normal, except for a slight increase in eosinophils. Through error, peripheral blood studies were not done at this time but 5 months after the acute phase of the disease the hemoglobin was 14.1 gm. and the total and differential leukocyte counts were normal. The erythrocyte indices had also returned to normal.

Case 2. A white man, aged 53, was admitted to Cushing Veterans Administration Hospital on November 30, 1950, because of extreme prostration and shortness of breath. His past history was revealing inasmuch as he had had previous hospitalization for over a year some 4 years earlier with a diagnosis of mental deterioration considered to be due to cerebral arteriosclerosis and bilateral cerebral cortical atrophy, the latter demonstrated by air encephalography. The record, obtained some time subsequent to his admission, revealed that during the first months of hospitalization his red blood cells numbered 3.5 to 3.8 million per cu.mm., with hemoglobin values of 10.8 to 11.8 gm. per 100 cc., and the volume of packed red blood cells 39 to 40%, with the mean corpuscular volume thus in the range 105 to 111 cu. microns. Treatment on the Neuropsychiatric Service was instituted with injections of both liver extract and iron without an endeavor to establish a specific response. Random blood examinations during later months, however, revealed maximum values of 4.8 million erythrocytes per cu.mm., 13.6 gm. of hemoglobin per 100 cc., and hematocrit of 41%.

For several years prior to the present admission the patient had lived alone in a rooming house, eating his meals here and there, and being seen infrequently by his family. He had had anorexia for a few months associated with increasing weakness. Substernal pain coming on with exertion and immediately relieved by rest had been present for several weeks. Although pneumonia was evident on entry, no date of onset could be determined. On the day before entry he "collapsed" in his room, where he was found to be pale and dyspneic the next day, when he was brought to the hospital.

On entry he appeared moribund, with rapid, labored respiration, extreme weakness, and marked pallor. He was disoriented and incoherent. The temperature was normal but subsequently rose to a maximum of 103.6° F. The pulse rate was 104, subsequently rising to 122; respirations were 30 to 40. Blood pressure was 100 mm. Hg systolic, 70 diastolic. The tongue was smooth at the edges. Evidence of consolidation of the right lower lobe was present. The heart was enlarged but otherwise normal. Minimal ankle edema was noted. At a later date when his mental state had improved it was noted that vibration was poorly perceived in the tibiae. Otherwise neurologic examination was negative.

The red blood cells numbered 0.71 million per cu.mm., the hemoglobin was 2.4 gm. per 100 cc., the hematocrit 8.0%, and the white blood cells 1,750 per cu. mm. with 65% segmented neutrophils, 1% band forms, 33% small lymphocytes, and 1% monocytes. The mean corpuscular volume was 112 cu. microns. There was marked variation in the size and shape of the erythrocytes with some tiny microcytes and some large oval cells well filled with hemoglobin. The neutrophils were hypersegmented. Platelets were exceedingly sparse (Table 3). The presumptive diagnosis was pernicious anemia.

Administration of oxygen and the transfusion of 1,500 cc. of citrated blood during the 12 hours following admission was associated with relief of dyspnea. In view of his critical condition and the blood findings, 45 mcg. of vitamin B_{12} were injected on the evening of admission and the administration of 600,000 units of penicillin daily was com-

menced. The following morning sternal bone marrow aspiration was performed (9 hours after vitamin B_{12} had been given) with the finding of a very cellular marrow in which there was a marked increase in cells of the granulocytic series (Fig. 2). A few blast forms were seen, but in view of the intensely myelocytic nature of the marrow they were considered to be of the myeloid series. The differential count is shown in Table 2. The diagnosis of aleukemic myelogenous leukemia was suggested. The continued febrile course led to the addition of aureomycin, 2 gm. daily, 48 hours later. On the sixth day the temperature fell to 100° F., and the reticulocytes rose to 1.8%. On this day repeat bone marrow aspiration showed an intensely normoblastic marrow, quite characteristic of commencing remission in pernicious anemia. The subsequent course was entirely uneventful. Vitamin B_{12} in 45 mcg. doses was injected weekly. With the clearing of his acute disorientation it was apparent that considerable mental deterioration was present. On discharge from the hospital 51 days after admission the bone marrow appeared normal. Blood values are shown in Table 3.

Laboratory data included initial urinalysis. This showed a trace of albumin, a few red and white blood cells, and numerous hyaline as well as finely and coarsely granular casts in the sediment. Following remission the urine became negative and the blood non-protein nitrogen fell from an initial 81 to 41 mg. per 100 cc. Urine cultures were sterile. Stools were repeatedly negative for occult blood. Post-histamine gastric anacidity was present. Serum chloride, 95 mEq./L. on entry, rose to 100. Total serum protein was 6.2 gm. per 100 cc. The van den Bergh test showed 0.9 mg. direct and 2.0 mg. indirect. Blood cultures showed no growth, and no pathogenic organisms were grown from the sputum.

TABLE 3.—BLOOD FINDINGS IN CASE 2

Date	RBC millions/ cu.mm.	Hbn.† gm./ 100 cc.	Het.‡ %	Reticulocytes %	WBC thousands/ cu.mm.	Differential Leukocyte Counts: Percentages					
						Neutrophils		Eosinophils	Basophils	Lymphocytes	Monocytes
						Segmented	Band Forms				
Nov. 30	0.71	2.4	8.0	0.1	1.75	65	1	0	0	33	1
Dec. 1	1.03	3.8	11.2	0.1	1.15	66	1	0	0	32	1
2				0.1							
3				0.1							
4	1.63	5.2	17.0	0.1	2.35	42	5	9	0	29	15
5				1.8							
6				5.0							
7				13.0							
8				14.0							
9				8.1							
10				7.4							
11	2.73	7.8	28.0	6.4							
12				5.6							
13	2.89	8.6	28.8	4.8	14.45	70	6	5	1	12	6
14				3.8							
15				3.4							
21	2.80	9.1	30.0	1.6	13.90						
28	3.66	10.2	35.2		8.85	65	5	4	4	19	3
an. 4	4.13	11.8	40.5		7.70	59	3	5	1	31	1
11	4.33	12.9	43.8		6.90	68	2	4	3	17	6
19	4.84	13.9	45.7		9.15	69	7	2	1	18	3
Feb. 19	5.51	14.8	48.0		8.50	58	4	2	1	30	5

† Hemoglobin
‡ Hematocrit
On Nov. 30 and Dec. 1 platelets were diminished on stained blood films. On Dec. 4 they were enumerated at 42,000/cu.mm. On Dec. 13 and thereafter they appeared normal in number on stained blood films.

Roentgen-ray examination of the chest on entry showed pneumonia in the right lower lobe and cardiac dilatation. Later the lungs were clear and the heart of normal size. Gastrointestinal Roentgen study was negative save for a small hiatus hernia. Electrocardiogram showed right bundle branch block and changes consistent with myocardial ischemia. The bundle branch block was not present after remission was well established.

Discussion. Although the occurrence of leukopenia and thrombocytopenia in pernicious anemia in relapse is well

known, whether there is an actual diminution in white-cell and platelet-forming centers in the marrow is still a matter of controversy[4]. Although it has often been assumed that the oligocythemia of pernicious anemia is due to a blocking of the marrow with megaloblasts, L. S. P. Davidson and Gulland[2] suggested that there was a lack of a leukocyte maturation factor. The correctness of this view seems to have been demonstrated by C. S. Davidson and his associates[1]. They transfused sufficient erythrocytes into patients with pernicious anemia in relapse to relieve completely the anemia, and, concomitantly, all those manifestations of the disorder due to the lowered oxygen carrying capacity of the blood. The megaloblastic marrow reverted to normal, but there was no change in leukocytes or platelets. The administration of liver extract was necessary to restore the white blood cells and platelets to normal, as well as to relieve those manifestations of the disease not primarily due to a low hemoglobin level. Further evidence for a disorder in leukopoiesis is at hand in the fact that giant metamyelocytes, possibly the precursors of the macropolycytes of the peripheral blood[4], are readily found in the marrow in relapse.

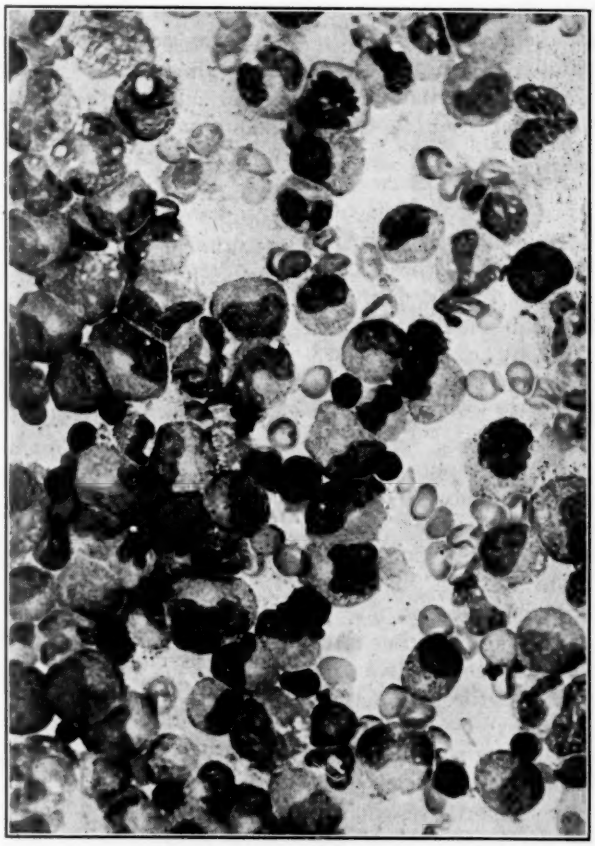

FIG. 2.—Bone marrow film in Case 2.

In the cases described above it may well be that infection served as the stimulus for excessive leukocyte production and caused the extensive myelocytic proliferation in the marrow; possibly because of the absence of a necessary maturation factor, these cells failed to develop into adult leukocytes. Similarly in pernicious anemia there is reason to believe that the hypoxemia caused by the anemia leads to the extensive megaloblastic proliferation which, in the absence of vitamin B_{12}, fails to lead to adequate red blood cell production[1].

Why, in the cases under discussion, megaloblasts were so sparse, is not clear. It may be that infection can inhibit the development of these cells from their precursors, or that granulocytic hyperplasia can block the marrow, as suggested by Ehrenfeld and de Vries[3] in their recent report of a case similar to those above except for the presence of leukocytosis.

The fact that the bone marrow may resemble that in myelogenous leukemia when a deficiency of vitamin B_{12} is present, together with infection, must bring to mind the thought that true myelogenous leukemia may be due to lack of a maturation factor rather than to a true neoplastic process. Obviously this factor is not the erythrocyte maturing principle since extensive employment of liver extract has shown that it is without effect in leukemia.

Completed case reports frequently fail to impress the reader with the diagnostic problems presented early in the patients' study. In the above cases, with all the data at hand, there appears to be no problem. In each, however, at the time of bone marrow examination the diagnosis was far from clear, and when the marrow films revealed a picture suggestive of myelogenous leukemia, this diagnosis was seriously entertained. In the first case, vitamin B_{12} was administered more as a gesture than as a specific therapeutic agent, and in the second case, it had been given before bone marrow examination because the critical condition of the patient appeared to preclude complete diagnostic study prior to institution of therapy. It is obvious that the diagnostic "therapeutic trial," so commonly employed in obscure cases of anemia before the days of routine bone marrow examination, still has much to recommend it whenever any diagnostic doubt exists.

Summary and Conclusion. Two patients with Addisonian pernicious anemia complicated by infection presented bone marrow pictures characterized by intense granulocytic activity and almost devoid of megaloblasts. In each the diagnosis of aleukemic myelogenous leukemia was considered. Both responded uneventfully to vitamin B_{12} therapy and subsequently exhibited entirely normal marrows. It is concluded that the bone marrow in pernicious anemia in relapse is not always pathognomonic.

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PERNICIOUS ANEMIA SUPERSEDED BY POLYCYTHEMIA VERA: REPORT OF A CASE

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It is well recognized that a slightly excessive erythrocytic response may occur as a consequence of adequate therapy in pernicious anemia[5]. However, the development of polycythemia vera in a patient being treated for pernicious anemia seems to be distinctly uncommon. Previously reported, well-documented cases seem to be rare.

The statistical probability of the 2 diseases occurring in one patient, however slight, must be recognized. Hence, previous articles reporting such an occurrence may well be valid, and we regret that decisive diagnostic criteria and methods currently attainable have understandably been lacking.

The case reported by Birnie[3] offers the best example previously available in the literature. On careful study of other similar cases, we do not believe that the rigid criteria necessary to secure a diagnosis of both conditions have been achieved[6].

Strauss[4] (in a forthcoming publication) describes the inverse of our case. A patient with polycythemia vera developed an anemia morphologically similar to pernicious anemia during the course of treatment by venesection. The patient responded characteristically to administration of liver extract. Polycythemia did not recur.

Avery's[1] report of a somewhat similar circumstance is not thoroughly convincing in the light of present day knowledge.

Case Report. A white female, aged 73 years, was seen in the office on August 1, 1950, with complaints of weakness and fatigability for approximately 1 year, shortness of breath on minimal activity for 2 months, massive swelling of the feet and legs for about 2 months, and enuresis and poor control of the bladder bordering on incontinence for 4 to 6 weeks. For an indefinite period, the patient had had difficulty in keeping her equilibrium.

Ten years previously, the patient had been told that she had "high blood pressure", but there was no follow-through of study or treatment. In April of 1947 she had undergone a panhysterectomy. The diagnosis was adenocarcinoma of the body of the uterus, grade 3. One month prior to our consultation, the administration of crude leaf digitalis, aminophylline, and a proprietary hematinic containing homeopathic proportions of numerous "anti-anemic factors" was begun. No improvement was noted in the complaints.

Examination by the operating surgeon (Dr. Robert F. Short, Jr.) on August 1, 1950, revealed no evidence of the recurrence or metastasis of the uterine carcinoma.

On initial examination, the patient appeared obviously fatigued and sought support and balance in walking. Height was 5 feet, 2 inches; weight, 136½ pounds; blood pressure, 160/60; temperature, 98.2°; and pulse, 78. The papillae of the dorsum of the tongue were decreased, and the lateral margins were

totally smooth. A nodule, 2 cm. in diameter, was found in the right lobe of the thyroid. It was freely movable and not very firm. The heart was normal in size, rate, and rhythm. A grade 1 systolic murmur was heard over all the precordium. Three-plus pitting edema extended from the dorsum of the feet to the knees. Vibratory perception (tuning fork 256 per second) was equivocally perceived in the upper third of each leg and was absent below that level bilaterally. Faint patellar, deep tendon reflexes were found.

The clinical diagnosis of pernicious anemia was made, and since a reticulocyte count of 2% was found, the patient entered Baylor University Hospital for further studies. The initial laboratory findings were: hemoglobin, 8.8 gm.; erythrocte count, 2,480,000; hematocrit, 28%; mean corpuscular volume, 112.9 cubic microns (cu. mc.); mean corpuscular hemoglobin, 35.5 mc.; mean corpuscular hemoglobin concentration, 31%; reticulocyte count, 3.2%, poikilocytosis and anisocytosis, marked; leukocyte count, 17,400 with 4% basophils, 3% eosinophils, 5% band neutrophils, 73% segmented neutrophils, and 15% lymphocytes; 1 normoblast per 100 leukocytes; gastric acidity (Ewald) free hydrochloric acid, zero; total acidity, 10 units; icterus index, 7; Bence-Jones protein (2 examinations), negative; Wassermann, Kahn, and Kline tests, negative.

The sternal marrow study revealed the following: erythroid series, 27.5% with 7 megaloblasts, 11.5 erythroblasts, and 9 normoblasts; myeloid series, 72.5% with 1 myeloblast, 39.5 myelocytes, 29.5 neutrophils; 2 eosinophils, and 0.5 lymphocytes. Normal cellularity and an increase in megaloblasts were noted.

An electrocardiogram employing standard limb leads, unipolar limb leads, and multiple precordial limb leads showed changes compatible with digitalis.

Anterior-posterior and lateral roentgenograms of the chest were not unusual.

On August 6, 1950, treatment for pernicious anemia was begun with daily injections of 30 mcg. of Vitamin B-12 and 2 cc. of crude liver extract (2 units per cc.). The response to treatment may be readily seen in the graph (Fig 1).

On August 24, 1950, the acceptable hemoglobin level and red cell count coupled with a complete neurological remission (vibratory perception being slight but definite) resulted in discontinuing the crude liver extract and in reducing the B-12 to 30 mcg. every other day for 3 doses, and then to 30 mcg. semiweekly.

On September 26, 1950, she was seen again in response to complaints of pain, swelling, and redness of the right leg of 2 days' duration. The lower ⅓ of the right leg was quite red, warm, and tender. The area of inflammation was rather sharply delineated, but streaks extended upward for several inches. This illness was thought to be erysipelas and superficial venous thrombosis. There was a slow but total remission on bed rest and penicillin therapy.

On October 17, 1950, she had an extremely florid complexion. She complained of not feeling well. The hemogram was markedly altered. (Palpation for the spleen and liver was not done at this time.) The blood pressure was 210/100. Anti-anemic therapy was discontinued from October 17 until her next visit, December 8. She was out of town in the meantime and had had more "erysipelas". No anti-anemic therapy was given after the week of October 17.

She was reexamined on January 24, 1951, and the blood counts and hemoglobin were found to have increased. She complained of an even redder complexion and of general malaise, dyspnea, and depression. Her legs had continued to trouble her with soreness and redness. Her spleen was enlarged, smooth, and firm, and extended well below the iliac crest.

Extensive Roentgen-ray studies were done. A summary of the roentgenological report revealed huge splenomegaly, slight congestion of the lung fields, slight but definite cardiac enlargement, possible thyroid nodule to the right of the trachea, and no abnormality of the skeletal system except osteoporosis compatible with the patient's age.

During the subsequent 2 months, the patient's previously noted subjective complaints worsened. Her rubor became more intense and the spleen was thought to be appreciably larger. Hematologic advances during this time are recorded in Fig. 1.

On March 5, 1951, it was unequivocally felt that the patient had developed a full-blown polycythemia. Accordingly, she was subjected to a phlebotomy with removal of 500 cc. and was given 7.5 mc. of radioactive phosphorus. Two and one-half weeks later, definite improvement in the patient's laboratory and clinical states seemed obvious. Periodic visits at semi-monthly intervals disclosed the same continuing trend. During this period of recovery, a blood volume determination amounted to 5.8 liters and was considered to be increased for the patient's size. Gastric analysis for free hydrochloric acid was repeated and again none was pres-

ent. A repeat bone marrow examination after onset of the polycythemia (Jan. 24, 1951) showed a complete change in the medullary picture with myeloid hyperplasia, some increase in megakaryocytes, and a persistently elevated percentage of erythroid forms of a more mature variety than formerly was noted (normoblasts and erythroblasts). No megaloblasts were seen.

ent in the anemic phase, evaluation of the bone marrow by Dr. O. P. Jones was in agreement with our findings of megaloblasts of the specific morphological type found in pernicious anemia. The extremely high hemoglobin and red blood cell values, leuko-

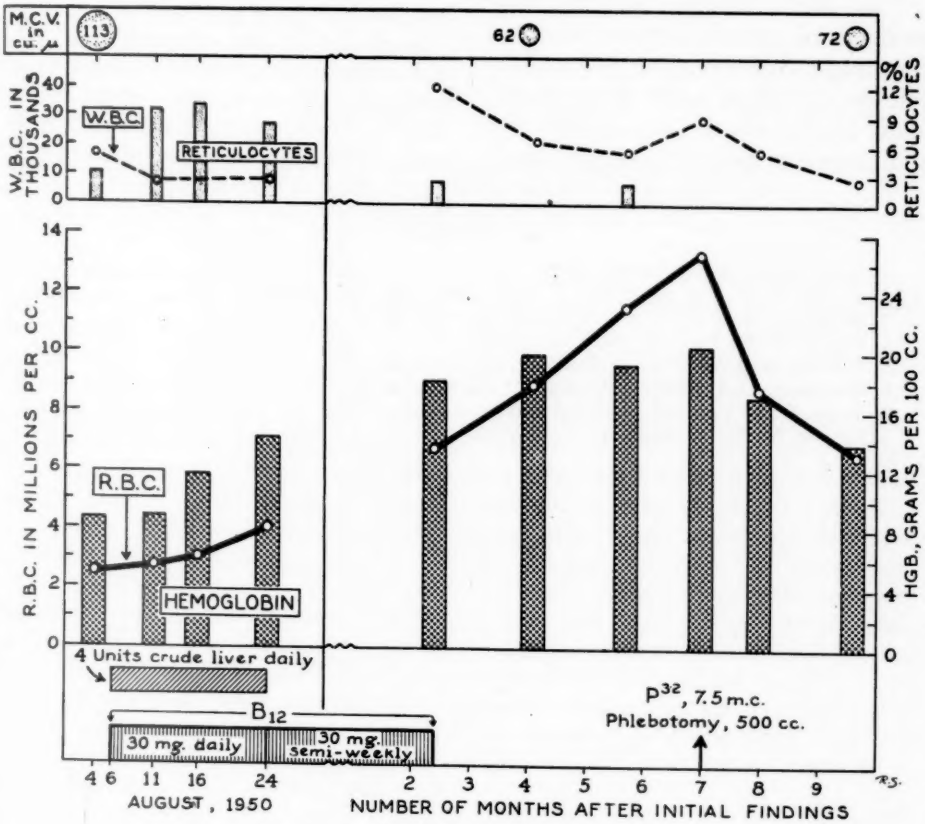

FIG. 1.—Graph depicting course of illness.

Since April, 1951, the patient has been almost free of symptoms. Findings on the last visit on May 28, 1951, revealed virtually complete remission in hematological findings as indicated. Rubor has completely disappeared, but the spleen has remained greatly enlarged.

Discussion. That both pernicious anemia and polycythemia vera existed seems unequivocal. In addition to the classical diagnostic findings being present in the anemic phase, evaluation of the bone marrow by Dr. O. P. Jones was in agreement with our findings of megaloblasts of the specific morphological type found in pernicious anemia. The extremely high hemoglobin and red blood cell values, leukocytosis, increased blood volume, splenomegaly, and the state of panmyelosis subsequently noted in the bone marrow seemed to justify fully the diagnosis.

Speculation at the present time in regard to this unusual association of these diseases has little basis in known facts. It has been suggested[4], however, that when they do co-exist, the basic

stimulus for medullary over-production prevailing in polycythemia is present but that the nutrient factor involved in clinically established pernicious anemia would hinder any polycythemic response. Only upon administration of the missing anti-anemic factor could the polycythemia then emerge.

One could surmise that excessive amounts of specific anti-anemic therapy might over-stimulate the marrow into producing an overt polycythemic state. Except for the occasionally dissimilar circumstance of a slightly over-reactive erythrocytic response, previously mentioned, there is nothing to substantiate this.

Some investigators have theorized that primary polycythemia is the antithesis[2] of pernicious anemia with the over-production of cells being due to excessive formation of hematopoietic factor. Experimental attempts to demonstrate this have not been convincing.

Summary. A case of pernicious anemia superseded by polycythemia vera is reported. From a review of the available literature, this circumstance would seem to be extremely uncommon.

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THE RELATION OF SERUM POTASSIUM TO ERYTHROCYTE POTASSIUM IN NORMAL SUBJECTS AND PATIENTS WITH POTASSIUM DEFICIENCY*

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THE concentration of potassium in the serum may, but does not necessarily, reflect the stage of depletion or repletion of intracellular potassium. Many of the symptoms of potassium deficiency may be due to low intracellular level rather than to the serum level itself[3]. A low serum potassium usually indicates an intracellular potassium deficit[27]. However, an intracellular deficit of potassium may sometimes occur with normal or high serum potassium[4]. The tissue potassium content, obtained by muscle biopsy[22] or calculated from balance studies[5], has been used to establish the presence of a deficiency in those cases with a normal serum potassium, but these are difficult determinations which are not usually available. The concentration of intracellular potassium in the red cells is easily and accurately determined with a flame photometer. Therefore, the relationship of the erythrocyte potassium concentration to the serum potassium level was studied in order to determine whether this relationship is an index of body potassium deficit.

Because of the widely varying ranges reported in the literature for normal serum and whole blood potassium, the concentration of serum potassium was determined in 177 individuals and the concentration of whole blood and erythrocyte potassium in 99 individuals, and normal ranges were established. The same determinations were performed on two groups of patients: one with hypopotassemia and the other with normal serum potassium in whom potassium deficits were suspected from the clinical picture. The data from these two groups of patients are compared with the normal. Intravenous potassium chloride was administered to those patients found to have a potassium deficiency. The relationship of the serum to the erythrocyte potassium following this therapy is presented.

Methods. Serum and whole blood potassium concentrations were determined on a flame photometer, with lithium as an internal standard[24]. The volume of packed red cells was determined according to the method of Musser and Wintrobe[23]. Concentrations of potassium per liter of erythrocytes were computed by means of the following formula:

$$K_c = \frac{K_b - (1 - V_c) \times K_s}{V_c}$$

where K_C, K_b, and K_s are the erythrocyte, whole blood, and serum potassium concentrations, respectively, in milliequivalents per

* Aided by a grant from the Jerome D. Solomon Memorial Research Foundation.

liter, and V_C is the hematocrit value expressed as a fraction of 1.

Results. A. Normal Values. *Serum Potassium.* Serum Potassium concentrations were determined in 177 normal, ambulatory adults (blood donors). The samples were taken at the termination of the blood donation from the last column of blood in the collecting tube. This blood was allowed to drain off by gravity into test tubes after removal of the needle from the transfusion-collecting flask. The clot was allowed to contract and the serum was obtained by centrifugation, after which the supernatant serum was removed and re-centrifuged. Any specimen showing hemolysis was discarded.

The frequency distribution of the serum potassium concentrations is pre-

TABLE 1.—FREQUENCY DISTRIBUTION OF SERUM POTASSIUM CONCENTRATION IN 177 NORMAL SUBJECTS

Serum Potassium mEq./L.	*No. of Subjects*	*Serum Potassium mEq./L.*	*No. of Subjects*
3.4	1	5.1	13
3.7	1	5.2	6
3.8	5	5.3	7
3.9	4	5.4	4
4.0	5	5.5	7
4.1	5	5.6	5
4.2	7	5.7	3
4.3	9	5.8	3
4.4	6	5.9	4
4.5	11	6.0	4
4.6	13	6.2	1
4.7	10	6.3	1
4.8	8	6.4	1
4.9	19		
5.0	14		

Average: 4.84 mEq./L.

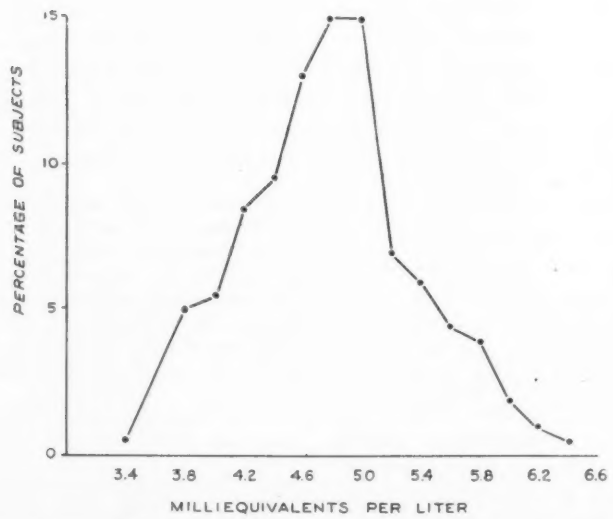

Fig. 1—Percentage frequency distribution of serum potassium concentration in 177 normal subjects. (Average concentration 4.84 mEq./L).

sented in Table 1. The average concentration was 4.84 mEq. per liter. The percentage frequency distribution and percentage ranges of the determinations are illustrated in Figs. 1 and 2. The serum potassium concentration in 75% of the subjects ranged from 4.1 to 5.6 mEq. per liter, and in 90% of the subjects it ranged from 3.9 to 5.8 mEq. per liter.

Whole Blood and Erythrocyte Potassium. The distribution of potassium between the serum and erythrocytes was studied in another 99 normal adults. Whole blood potassium analyses were performed on venous blood, withdrawn by syringe, to which sodium oxalate had been added as an anticoagulant.* The sodium oxalate contained no detectable potassium. Serum

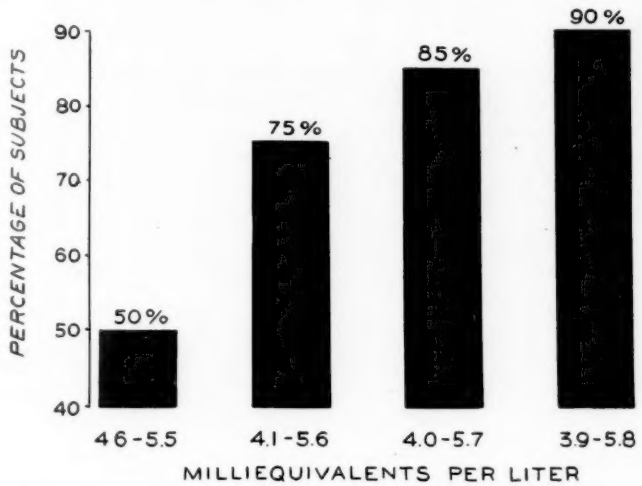

FIG. 2.—Ranges of serum potassium concentration in 177 normal subjects.

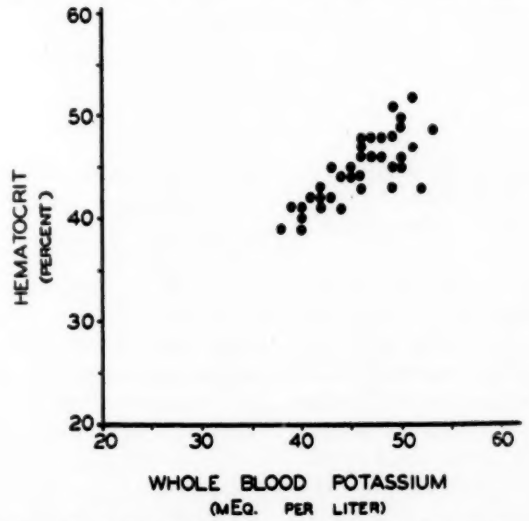

FIG. 3.—Relation of whole blood potassium concentration to hematocrit value.

* 5 cc. of blood and 6 mg. of sodium oxalate.

analyses were performed on separate samples of serum from clotted blood which had been doubly centrifuged.

The serum potassium was within the normal range in all subjects. The potassium content of the whole blood specimens varied directly with the hematocrit (Fig. 3). The whole blood potassium concentration ranged from 40.0 to 53.0 and averaged 45.5 mEq. per liter.

Hypopotassemic Patients: Distribution of potassium between the serum and erythrocytes was studied in 42 patients with hypopotassemia. Etiologic factors and symptoms of potassium deficiency were prominent in all cases[18]. The clinical diagnoses and serum, whole blood, and erythrocyte potassium concentrations on admission are presented in Table 3. All the patients had a serum potassium below 3.9 mEq. per

TABLE 2.—WHOLE BLOOD, SERUM AND RED CELL POTASSIUM CONCENTRATIONS IN PATIENTS WITH ANEMIA

Serum K mEq./L.	*Whole Blood K mEq./L.*	*Hematocrit % R.B.C.*	*Red Cell K mEq./L.*
4.7	38	33	108.6
4.2	34	34	92.0
4.9	40	36	102.0
5.3	41	38	99.2
4.1	32	31	94.2
5.0	30	30	88.4
5.0	38	37	94.6
4.0	35	36	90.3
4.3	34	35	89.2
4.6	33	32	93.3
5.0	40	39	94.7
4.7	38	33	105.5
5.5	41	37	100.1
5.0	38	37	94.2
4.5	40	39	95.4
5.2	42	37	104.3
5.0	41	36	104.9
4.2	35	34	95.3
4.2	33	30	100.0
4.9	37	35	99.9
5.6	32	29	96.5
4.7	34	34	91.2
4.1	33	32	94.3

The concentration of potassium per liter of packed erythrocytes ranged from 93.6 to 115.8 and averaged 99.2 mEq. per liter.

Effects of Anemia on Serum, Whole Blood, and Erythrocyte Potassium. Twenty-three subjects with iron deficiency anemia were studied. The whole blood potassium was below the normal range in all subjects. However, the values for both serum and erythrocyte potassium were within the range of normal (Table 2).

B. PATIENTS WITH POTASSIUM DEFICIENCY. *Erythrocyte Potassium in* liter. Twenty-five patients (59.5%) had an erythrocyte potassium below the normal range.

Two patients of a group of 9 with symptoms of potassium deficiency and large volume losses of gastrointestinal fluids due to vomiting had a normal serum potassium on admission but a low concentration of erythrocyte potassium. Following hydration with saline and glucose solutions, the serum potassium in these 2 patients was also definitely below the normal range.

Postoperative Changes in Serum and Erythrocyte Potassium. Progressive

TABLE 3.—SERUM, WHOLE BLOOD, AND ERYTHROCYTE POTASSIUM CONCENTRATIONS IN PATIENTS WITH HYPOPOTASSEMIA

Diagnosis	*Serum K mEq./L.*	*Whole Blood K mEq./L.*	*Hematocrit % R.B.C.*	*Red Cell K mEq./L.†*
Small bowel obstruction	3.6	40	45	84.3*
" " "	2.8	42	45	89.9*
" " "	3.2	56	60	91.3*
" " "	3.8	44	46	91.2*
" " "	3.3	51	52	94.9
" " "	2.9	24	23	94.7
" " "	3.1	41	41	95.5
" " "	2.7	36	41	83.8*
" " "	2.7	44	46	92.3*
" " "	3.0	49	46	103.0
Large bowel obstruction	3.8	40	37	100.1
" " "	3.4	46	44	100.2
" " "	3.8	43	50	82.2*
" " "	3.4	45	45	96.0
Large bowel fistula	3.2	43	40	97.5
Total gastrectomy	3.2	49	58	82.3*
" "	2.7	41	40	98.5
" "	3.5	41	47	83.4*
Bleeding peptic ulcer	3.1	41	41	95.5
" " "	2.6	29	32	85.0*
Perforated peptic ulcer	3.1	39	42	92.3*
" " "	3.9	38	41	87.1*
" " "	3.7	44	46	91.2*
Regional ileitis	3.6	40	43	85.8*
Incar. umbilical hernia	2.8	48	45	103.2
Appendiceal abcess	3.8	40	33	112.4
Pyloric obstruction	2.3	32	40	76.5*
" "	3.6	39	44	84.0*
" "	3.3	38	39	92.3*
" "	3.2	44	50	84.8*
" "	3.1	36	38	89.5*
Carcinoma of stomach	2.7	41	40	98.5
" " "	3.8	32	34	86.8*
Carcinoma of esophagus	2.8	40	34	112.2
Esophagectomy	3.4	46	44	100.2
Acute cholecystitis	3.1	36	42	81.4*
Acute pancreatitis	3.7	47	43	104.6
" "	3.6	40	42	90.2*
" "	3.6	48	47	98.0
Hemicolectomy	3.5	41	47	83.8*
Abdominoperineal resection	2.9	24	27	81.1*
Small bowel fistula	3.5	48	54	85.7*
Cecal fistula	3.4	43	46	89.7*
Cecostomy	2.8	38	42	86.5*
Tuboovarian abscess	2.8	41	47	84.0*
" "	3.8	40	34	112.2
Hyperemesis gravidarum	2.6	41	48	82.7*
" "	2.9	34	37	87.0*
" "	3.9	41	40	96.8

* Below normal range
† Per liter packed erythrocytes

changes in serum and erythrocyte potassium were studied in 7 patients allowed to develop a potassium deficiency postoperatively. These patients were on continuous Levin suction and received potassium-free intravenous fluids. Serum potassium levels below 3.5 mEq. per liter developed in all 7 patients before the 7th postoperative day. Erythrocyte potassium showed a moderate to marked fall in 5 patients. Hypopotassemia was present 3 to 5 days before the appearance of decreased erythrocyte potassium.

Serum and Erythrocyte Potassium Following Administration of KCl. Potassium chloride* was administered intravenously to 15 normal subjects and 37 of the above patients. The normal subjects received 6 gm. daily for 4 days. The patients received an average of 12 gm. daily until the serum potassium was normal for 24 hours. Serum and whole blood potassium were determined daily. Blood was drawn in the morning under fasting conditions before the day's fluid therapy was started.

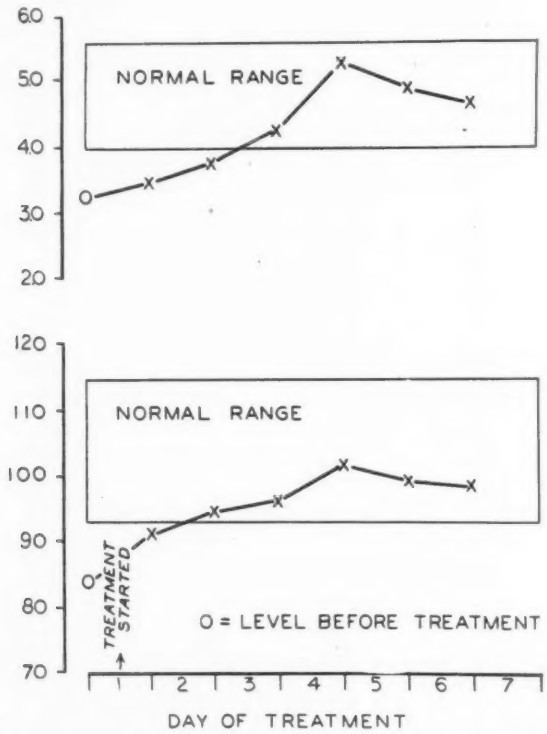

FIG. 4.—Effect of intravenous KCl on serum and erythrocyte potassium. (Average of 23 patients). Average of 12 gm. of KCl daily until 5th day. Serum and erythrocyte potassium determined from blood specimen drawn in the morning under fasting conditions before the day's fluid therapy had been started. Ordinates: Upper graph, serum potassium mEq./L.; lower graph, erythrocyte potassium mEq./L.

No significant change in serum or erythrocyte potassium was observed in the normal subjects. The erythrocyte potassium was not significantly

* As 2 to 3 gm. of KCl in 1000 cc. of 5% dextrose or 0.9% sodium chloride solution.

altered in 14 patients with initial normal erythrocyte levels, although the serum level was raised to normal. In 23 patients with initial abnormally low erythrocyte potassium, the erythrocyte concentration was raised to normal within 48 hours and usually before the serum potassium returned to normal (Fig. 4).

TABLE 4.—NORMAL RANGE OF SERUM POTASSIUM AS REPORTED IN THE LITERATURE

Author	*Year*	*Number of Determinations*	*Serum Potassium (mEq./L.)*	*Method*
Kramer and Tisdall[16]	1921	10 16	4.8–5.1 (4.1) 4.6–5.4 (4.2)	Unashed serum Ashed serum
Meyers and Short[20]	1921	4	3.6–4.6	Ash method
Atchley, Loeb, Benedict and Palmer[2]	1923	6	3.1–5.2	Precipitation method
Hoffman and Jacobs[14]	1934	30	4.0–5.4 (4.7)	Colorimetric
Hald and Eisenman[10]	1937	16	3.4–6.5 (4.6)*	Dry ash
Albanese and Wagner[1]	1945	6	3.7–5.6	Colorimetric
Hald[11]	1946	8	3.1–5.3	Dry ash
Marinis, Muirhead, Jones and Hill[19]	1947	107	3.6–6.2 (4.5) 4.2–4.8 (75%) 3.9–5.1 (93%)	Flame Photometric*
Hald[12]	1947	5 5	4.2–4.9 3.8–4.8	Flame Photometric* Chemical
Randall, Habif, Lockwood and Werner[25]	1949	35	4.26	Flame Photometric
Lans, Stein and Meyer	1951	177	(4.84) 4.1–5.6 (75%) 3.9–5.8 (90%)	Flame Photometric†

* Experimental model of flame photometer.
† Perkin Elmer Model 52C flame photometer. Reproducible accuracy of within 1%.

Discussion. The earliest recorded figures for the concentration of cations and anions in human blood are those reported by Schmidt in 1850[26]. More recent reports of the normal serum potassium have usually been based on a small number of determinations and have reported widely varying ranges (Table 4). The ranges reported for erythrocyte and whole blood potassium have likewise been based on a small number of determinations (Table 5). These previous studies were the result of the development of various chemical methods of analysis. The flame photometer now offers a rapid means of accurately determining the concentration of potassium in biologic media. The instrument used in this study* has a reproducible accuracy of within 1%. Our figures for serum potassium agree closely with those reported by Hoffman and Jacobs who used a colorimetric method which is accurate, but very time consuming.

Recent case reports of potassium deficiency have stated wide ranges for

* Perkin-Elmer Model 52C.

normal serum potassium. Our study, however, demonstrates that the serum potassium normally varies within a small range. The frequency distribution of the determinations conforms to the normal probability curve.

As illustrated in Fig. 3, the whole blood potassium varies directly with the hematocrit value. However, when the potassium content of the erythrocyte is calculated, the constancy of the corpuscular potassium content becomes apparent. This is about 20 times the concentration of the same element in serum.

mental animals[6]. The low potassium concentration of the erythrocytes and the restoration of normal erythrocyte potassium following administration of potassium chloride reflects the potassium depletion of the body cells in the patients in the present study.

Experiments with radioactive potassium (K^{42}) have shown that there exists a continuous exchange of potassium between the intracellular and the extracellular phases of most tissues including the erythrocytes[13]. A net transport of potassium into the erythrocyte has been shown by *in vitro* experiments

TABLE 5.—NORMAL RANGE OF WHOLE BLOOD AND ERYTHROCYTE POTASSIUM AS REPORTED IN THE LITERATURE

Author	*Year*	*Number of Determinations*	*Whole Blood Potassium (mEq./L.)*	*Erythrocyte Potassium (mEq./L.*)*	*Method*
Kramer and Tisdall[17]	1922	13	39.2–51.9 (46.6)	105.1–113.9 (109.7)	Ashed serum
Hoffman and Jacobs[14]	1934	30	43.4–55.9	100.8–118.6 (108.3)	Colorimetric
Hald and Eisenman[10]	1937	16	36.4–49.6	72.0–102.0 (83.0)	Dry ash method
Lans, Stein and Meyer	1951	99	40.0–53.0 (45.5)	93.6–115.8 (99.2)	Flame Photometric

* Per liter packed erythrocytes.

Low potassium concentration of the erythrocytes has been stated to be an unusual finding even in potassium deficiency[7]. Kennedy[15] has reported 1 case, and Eliel[8] 4 cases, of low erythrocyte potassium in patients with hypokaliemic alkalosis. In the present study, 25 of a group of 42 hypopotassemic patients were found to have abnormally low erythrocyte potassium concentrations. The incidence of alteration of erythrocyte potassium in potassium deficiency is therefore probably greater than has been previously stated.

A lowering of potassium in muscle cells has been repeatedly demonstrated in hypopotassemic patients[4,22] and in induced potassium deficits in experi-

to occur only in erythrocytes with abnormally low potassium content[9]. That this is also true *in vivo* is demonstrated by the absence of significant change in erythrocyte potassium following intravenous administration of relatively large amounts of potassium chloride to 15 normal subjects.

The rate of penetration of labeled potassium into the erythrocyte has been shown to be relatively low compared with that of other human tissue cells[21]. Therefore, when the erythrocyte potassium has been restored to normal following administration of potassium salts, repletion of general body potassium will have been well instituted.

Since in the present study only 59.5% of a group of 42 patients with definite body deficits of potassium had abnormally low concentrations of erythrocyte potassium, a normal erythrocyte potassium does not exclude the presence of a potassium deficiency. Furthermore, we have found in our previous studies on potassium metabolism[18] that a hypopotassemia is usually present in surgical patients with a potassium deficiency. Therefore, determination of the whole blood potassium is probably indicated for the diagnosis of potassium deficiency only under certain circumstances.

It has been stated in the literature that severely dehydrated patients may have marked intracellular deficits of potassium but a normal serum potassium. In these patients the erythrocyte potassium determination may be of value for the diagnosis of a potassium deficiency. This is demonstrated by 2 dehydrated patients in the present study, where the finding of a lowered erythrocyte potassium was indicative of a potassium deficiency and the true state of the serum potassium was disclosed following hydration with saline and glucose solutions.

Summary and Conclusions. 1. Serum potassium was determined in 177 normal subjects. The average concentration was 4.84 mEq. per liter. The range in 75% of the subjects was from 4.1 to 5.6 mEq. per liter; in 85% from 4.0 to 5.7 mEq. per liter, and in 90% from 3.9 to 5.8 mEq. per liter.

2. The distribution of potassium between the serum and erythrocytes was studied in another 99 normal adults. Whole blood potassium ranged from 40.0 to 53.0 and averaged 45.5 mEq. per liter. Concentration of potassium per liter of packed erythrocytes ranged from 93.6 to 115.8 and averaged 99.2 mEq. per liter.

3. Whole blood potassium was below normal range in 23 anemic subjects. However, the values for both serum and erythrocyte potassium were normal.

4. Twenty-five of a group of 42 hypopotassemic patients were found to have abnormally low concentrations of erythrocyte potassium.

5. Intravenously administered potassium chloride had no effect on erythrocyte potassium in 15 normal subjects. In 23 hypopotassemic patients with initial abnormally low erythrocyte potassium, the erythrocyte concentration was raised to normal usually within 48 hours following institution of intravenous administration of potassium chloride.

6. In general, the serum potassium determination is a more frequent index of body potassium deficit than the erythrocyte potassium determination. However, in dehydrated patients with potassium deficiency, a low erythrocyte level may appear before a low serum level.

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THE EFFECT OF SUBOPTIMAL CONCENTRATIONS OF ANTICOAGULANT SOLUTIONS UPON THE CLOTTING TIMES OF NORMAL AND HYPOPROTHROMBINEMIC HUMAN AND DOG BLOOD

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According to an observation made by Quick and Stefanini[9], tricalcium phosphate does not adsorb prothrombin from citrated plasma. From this finding they derived the conclusion that citrate unites with prothrombin to the extent that tricalcium phosphate is unable to remove prothrombin from the plasma. Assuming that such a union prevents the clotting of blood, the hypothesis was advanced that in hypoprothrombinemia, a lesser concentration of sodium citrate may be sufficient to suspend or delay coagulation as compared with normal plasma. If such a delay of coagulation upon addition of suboptimal amounts of anticoagulant could be found, it may perhaps be regarded, in a general way, as evidence of hypoprothrombinemia. In order to verify this theory, experiments were carried out in which a given amount of venous blood from normal and dicoumarinized patients, as well as from normal and dicoumarinized dogs, was added to varying amounts of a given suboptimal concentration of sodium citrate. The clotting time was then determined on each specimen. Subsequently the experiments were extended to include sodium oxalate as well.

Materials and Methods: Solutions of 0.01 molar sodium citrate and 0.01 molar sodium oxalate were prepared; also a mixture of equal parts of 0.01 molar sodium citrate and 0.01 molar sodium oxalate. In the experiments with sodium citrate blood from 20 normal individuals and 20 dicoumarinized patients was distributed in quantities of 1 cc. each into 7 tubes measuring 75 by 8 mm., labeled 1 to 7, and containing 0.2 cc., 0.3 cc., 0.42 cc., 0.44 cc., 0.46 cc., 0.48 cc. and 0.5 cc. of the anticoagulant, respectively. The identical procedure was carried out with blood from 10 normal individuals and 10 dicoumarinized patients which was distributed into a series of tubes containing 0.01 molar solution of sodium oxalate and another series of tubes containing a mixture of equal parts of 0.01 molar solution of sodium citrate and 0.01 molar solution of sodium oxalate. About 12 cc. of venous blood were withdrawn in each test, of which 7 cc. were placed in a large glass tube and rapidly transferred in quantities of 1 cc. into each of the 7 tubes by means of a 1 cc. blow-out pipette. A graduated centrifuge tube containing 0.5 cc. of 0.1 molar solution of sodium citrate was filled up to the 5 cc. mark with the rest of the venous blood for the determination of the prothrombin time. Each tube was gently inverted in order to permit immediate and thorough contact with the anticoagulant solution.

In the experiments with blood from 10 normal and 10 dicoumarinized dogs, each 1 of the 3 aforementioned anticoagulant solutions was distributed in a series of 5 tubes labeled 1 to 5, in the amounts of 0.3 cc., 0.4 cc., 0.5 cc., 0.6 cc., and 0.7 cc. About 7 cc. of venous blood were withdrawn, of which 5 cc. were placed in a large glass tube and rapidly pipetted off in quantities of 1 cc. into each of the 5 tubes containing the anticoagulant solution. The rest of the venous blood served to fill a graduated centrifuge tube containing 0.2 cc. of 0.1 molar solution of

sodium citrate up to the 2 cc. mark for the determination of prothrombin time.

For the determination of the clotting time. the tubes containing normal blood were inverted once every minute. The tubes containing hypoprothrombinemic blood were inverted every 10 minutes except those in Tubes 1 to 3, which were inverted once every minute because of their shorter clotting time. Whenever the blood stopped flowing upon inversion of the tube, the time was recorded.

Each dicoumarinized dog weighing about 10 Kg. received 25 mg. dicoumarin on 3 successive days which in most instances produced a prothrombin time of about 35 seconds on the 5th day. Specimens of blood yielding prolonged prothrombin times were withdrawn from the 2nd day on.

The prothrombin time of each blood specimen was determined according to the photoelectric modification of the 1-stage Quick method[3].

Results. The mean clotting time of normal human blood added to suboptimal amounts of sodium citrate, as established from 20 specimens, increased from 5.6 minutes in Tube 1 to 8.9 minutes in Tube 2, 16.5 minutes in Tube 3, 22.7 minutes in Tube 4, 29.6 minutes in Tube 5, 37.2 minutes in Tube 6, and 47.5 minutes in Tube 7 (Table 1). These results are shown in Fig. 1.

TABLE 1.—CLOTTING TIMES OF NORMAL AND HYPOPROTHROMBINEMIC HUMAN BLOOD ADDED TO SUBOPTIMAL AMOUNTS OF VARIOUS ANTICOAGULANT SOLUTIONS.

		Tube						
	*P.T.**	*No. 1*	*No. 2*	*No. 3*	*No. 4*	*No. 5*	*No. 6*	*No. 7*
		0.2 cc.	0.3 cc.	0.42 cc.	0.44 cc.	0.46 cc.	0.48 cc.	0.5 cc.
0.01 Molar Solution of Sodium Citrate Added to:								
A: Normal Human Blood								
Mean of 20 Serial Tests	13.5″	5.6′	8.9′	16.5′	22.7′	29.6′	37.2′	47.5′
Maximum	14.6″	8′	12′	23′	29′	39′	51′	63′
Minimum	12.1″	3′	5′	8′	13′	20′	22′	30′
B: Hypoprothrombinemic Human Blood								
Patient 2	15.9″	5′	10′	18′	30′	32′	1.1 hr.	2.25 hr.
Patient 7	17.0″	11′	19′	1.4 hr.	1.5 hr.	1.7 hr.	9.7 hr.	10.0 hr.
Patient 10	18.1″	8′	12′	1.3 hr.	1.5 hr.	10.6 hr.	11.6 hr.	18.0 hr.
Patient 12	18.4″	10′	17′	5.2 hr.	7.5 hr.	15.0 hr.	17.0 hr.	20.5 hr.
Patient 15	18.9″	10′	18′	42′	4.0 hr.	4.3 hr.	17.5 hr.	21.0 hr.
Mean of 20 Serial Tests	18.8″	8.8′	16.3′	2.9 hr.	5.9 hr.	12.5 hr.	14.7 hr.	19.7 hr.
0.01 Molar Solution of Sodium Oxalate Added to:								
A: Normal Human Blood								
Mean of 10 Serial Tests	13.6″	6.2′	8.4′	—	—	—	—	—
Maximum	14.2″	11′	∞	∞	∞	∞	∞	∞
Minimum	13.1″	4′	5′	5′	7′	7′	8′	8′
B: Hypoprothrombinemic Human Blood								
Mean of 10 Serial Tests	18.4″	7.9′	—	—	—	—	—	—
Maximum	22.5″	11′	∞	∞	∞	∞	∞	∞
Minimum	15.1″	6′	9′	∞	∞	∞	∞	∞
Mixture of Equal Parts of 0.01 Molar Solution of Sodium Citrate and 0.01 Molar Solution of Sodium Oxalate Added to:								
A: Normal Human Blood								
Mean of 10 Serial Tests	13.4″	6.2′	7.6′	9.0′	10.1′	10.9′	12.5′	13.8′
Maximum	13.9″	9′	10′	12′	13′	14′	16′	19′
Minimum	12.6″	4′	5′	6′	7′	7′	8′	9′
B: Hypoprothrombinemic Human Blood								
Patient 3	16.3″	4′	5′	6′	6′	6′	6′	6′
Patient 8	17.1″	8′	9′	10′	12′	13′	14′	19′
Patient 16	19.3″	5′	7′	10′	20′	22′	25′	29′
Patient 19	27.7″	10′	15′	30′	35′	35′	36′	45′
Patient 20	30.2″	10′	12′	40′	∞	∞	∞	∞
Mean of 10 Serial Tests	22.9″	7.7′	9.9′	18.6′	—	—	—	—

* Prothrombin time

The mean clotting time of normal human blood added to suboptimal amounts of sodium oxalate as established from 10 specimens was 6.2 minutes in Tube 1 and 8.4 minutes in Tube 2. Mean clotting times could not be established in the tubes with higher numbers since the blood remained fluid indefinitely in a number of tubes. A sudden transition from a definite and relatively short clotting time to an infinitely long one was noted in many instances. The consistent and gradual increase of the clotting times observed upon addition of sodium citrate and as described above was absent in this series with sodium oxalate.

The mean clotting time of normal human blood added to suboptimal amounts of a mixture of equal parts of sodium citrate and sodium oxalate was 6.2 minutes in Tube 1, 7.6 minutes in Tube 2, 9.0 minutes in Tube 3, 10.1 minutes in Tube 4, 10.9 minutes in Tube 5, 12.5 minutes in Tube 6, and 13.8 minutes in Tube 7. In no instance was an infinitely prolonged clotting time observed (Table 1).

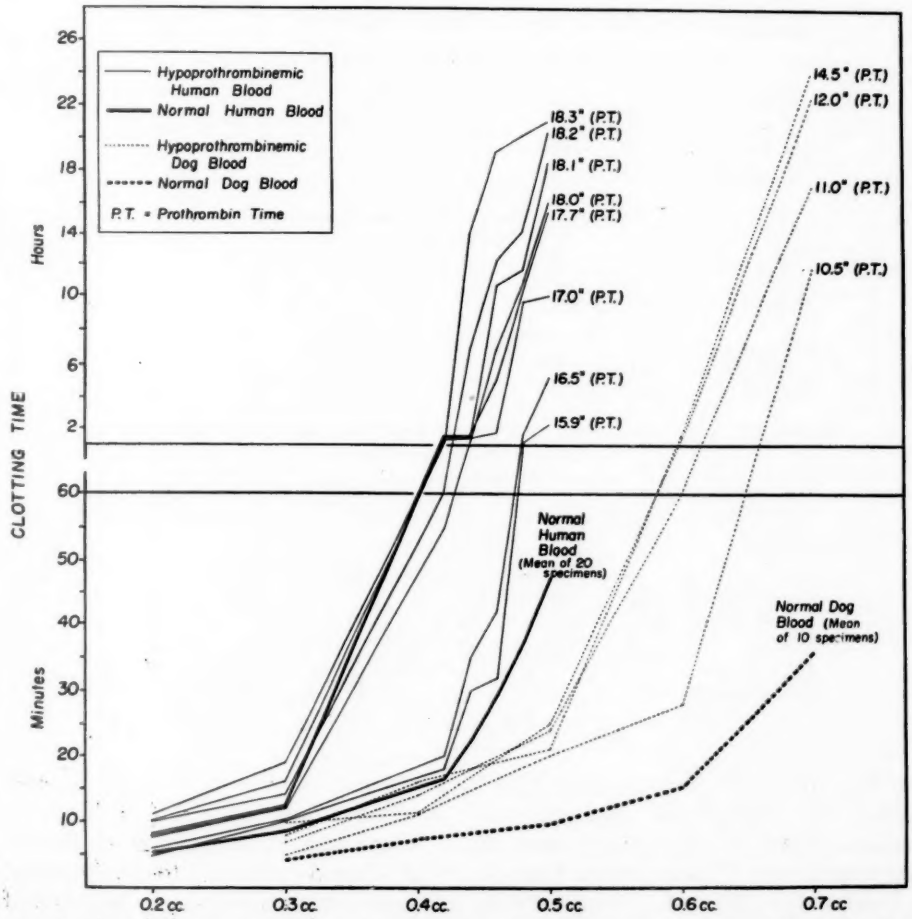

FIG. 1.—Clotting times of normal and hypoprothrombinemic human and dog blood added to suboptimal amounts of 0.01 molar solution of sodium citrate.

Normal dog blood yielded results similar to those obtained with human blood with each anticoagulant except for the fact that the clotting times were in general shorter than those of human blood (Fig. 1). Specifically, the mean clotting time of normal dog blood added to suboptimal amounts of sodium citrate, as established from 10 specimens, was 4.1 minutes in Tube 1, 7.1 minutes in Tube 2, 9.6 minutes in Tube 3, 15.0 minutes in Tube 4, and 35.6 minutes in Tube 5 (Table 2).

The mean clotting times of normal dog blood added to suboptimal amounts of sodium oxalate were 3.7 minutes in Tube 1, 5.4 minutes in Tube 2, and 8.0 minutes in Tube 3. Mean clotting times could not be established for Tubes 4 and 5 because several specimens failed to clot (Table 2).

The mean clotting times of normal dog blood added to suboptimal amounts of a mixture of equal parts of sodium oxalate and sodium citrate, as established from 10 specimens, were

TABLE 2.–CLOTTING TIMES OF NORMAL AND HYPOPROTHROMBINEMIC DOG BLOOD ADDED TO SUBOPTIMAL AMOUNTS OF VARIOUS ANTICOAGULANT SOLUTIONS.

	P.T.*	Tube No. 1	Tube No. 2	Tube No. 3	Tube No. 4	Tube No. 5
		0.3 cc.	0.4 cc.	0.5 cc.	0.6 cc.	0.7 cc.
0.01 Molar Solution of Sodium Citrate Added to:						
A: Normal Dog Blood						
Mean of 10 Serial Tests	7.3″	4.1′	7.1′	9.6′	15.0′	35.6′
Maximum	8.0″	6′	9′	12′	19′	45′
Minimum	6.8″	3′	5′	7′	11′	28′
B: Hypoprothrombinemic Dog Blood						
Dog 1	10.5″	5′	11′	20′	28′	11.7 hr.
Dog 2	12.0″	10′	11′	25′	1.3 hr.	22.4 hr.
Dog 4	14.6″	9′	18′	1.25 hr.	1.5 hr.	24.3 hr.
Dog 6	18.8″	18′	39′	1.5 hr.	23.0 hr.	27.2 hr.
Dog 9	31.3″	10′	15′	40′	21.7 hr.	∞
Mean of 10 Serial Tests	18.7″	11.5′	23.2′	—	—	—
0.01 Molar Solution of Sodium Oxalate Added to:						
A: Normal Dog Blood						
Mean of 10 Serial Tests	7.4″	3.7′	5.4′	8′	—	—
Maximum	7.8″	4′	10′	16′	28′	∞
Minimum	7.0″	3′	4′	5′	8′	13′
B: Hypoprothrombinemic Dog Blood						
Mean of 10 Serial Tests	22.3″	8.5′	—	—	—	—
Maximum	37.0″	19′	∞	∞	∞	∞
Minimum	11.9″	3′	4′	6′	8′	13′
Mixture of Equal Parts of 0.01 Molar Solution of Sodium Citrate and 0.01 Molar Solution of Sodium Oxalate Added to:						
A: Normal Dog Blood						
Mean of 10 Serial Tests	7.5″	3.4′	4.5′	5.3′	5.8′	6.6′
Maximum	7.8″	4′	5′	6′	7′	7′
Minimum	7.0″	3′	4′	5′	5′	6′
B: Hypoprothrombinemic Dog Blood						
Dog 3	14.4″	10′	10′	12′	12′	12′
Dog 5	15.6″	8′	8′	10′	11′	13′
Dog 7	19.0″	8′	9′	10′	10′	18′
Dog 8	21.9″	9′	16′	16′	18′	24′
Dog 10	33.3″	5′	6′	7′	19′	∞
Mean of 10 Serial Tests	19.4″	7.8′	9.3′	10.1′	11.9′	—

* Prothrombin time

3.4 minutes in Tube 1, 4.5 minutes in Tube 2, 5.3 minutes in Tube 3, 5.8 minutes in Tube 4, and 6.6 minutes in Tube 5 (Table 2). The graphic registration of these results yields a horizontal line in contrast to the curves obtained with sodium citrate (Fig. 2).

Hypoprothrombinemic human blood added to suboptimal amounts of sodium citrate yielded clotting times which were considerably prolonged if compared with the corresponding results obtained with euprothrombinemic human blood. The clotting times increased parellel with the prothrombin times as seen from Fig. 1. They also increased parallel with the amount of anticoagulant so that they were highest in Tube 7. The mean clotting times were: 8.8 minutes in Tube 1, 16.3 minutes in Tube 2, 2.9 hours in Tube 3, 5.9 hours in Tube 4, 12.5 hours in

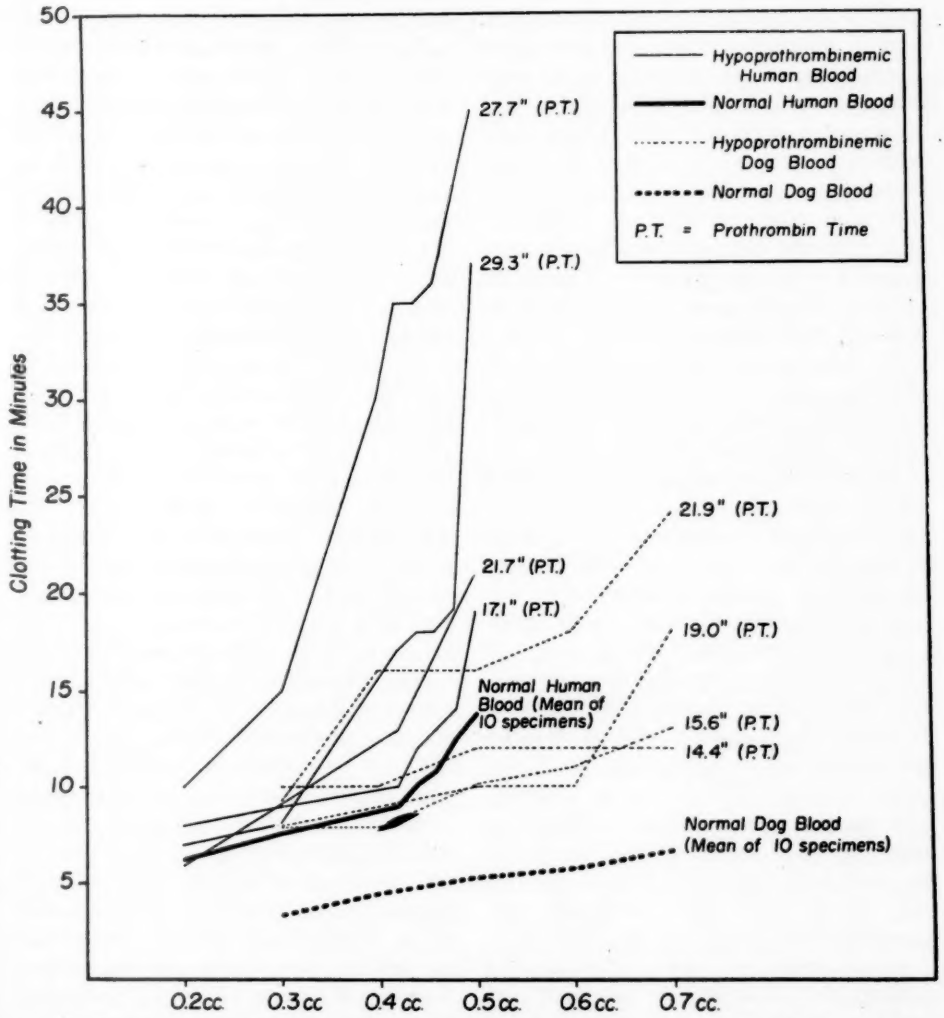

FIG. 2—Clotting times of normal and hypoprothrombinemic human and dog blood added to suboptimal amounts of a mixture of equal parts of 0.01 molar solution of sodium citrate and 0.01 molar solution of sodium oxalate.

Tube 5, 14.7 hours in Tube 6, and 19.7 hours in Tube 7. The mean prothrombin time of all 20 specimens was 18.8 seconds.

Hypoprothrombinemic human blood added to suboptimal amounts of sodium oxalate failed to clot in most instances except in Tube 1 where the mean clotting time was 7.9 minutes (Table 1).

Hypoprothrombinemic human blood added to suboptimal amounts of a mixture of sodium oxalate and sodium citrate yielded moderately prolonged clotting times which were most pronounced in Tube 7, the longest being 45 minutes obtained from a specimen with a prothrombin time of 27.7 seconds. Two specimens having a prothrombin time of 28.1 seconds and 30.2 seconds did not clot in the last 3 and 4 tubes, respectively. The mean clotting times were 7.7 minutes in Tube 1, 9.9 minutes in Tube 2, and 18.6 minutes in Tube 3. No mean clotting times were established in Tubes 4 to 7 because some specimens failed to clot (Table 1).

Hypoprothrombinemic dog blood added to suboptimal amounts of sodium citrate resulted in clotting times similar to those obtained with human blood. They paralleled the corresponding prothrombin time and also gradually increased with the amount of anticoagulant, so that the longest clotting times were observed in Tube 5. In some dogs having a considerably prolonged prothrombin time, the blood never clotted in Tube 4 or Tube 5, and in one dog with a prothrombin time of 19.0 seconds, the blood remained fluid indefinitely from the 3rd tube on. Some of these results are represented graphically in Fig. 1.

Hypoprothrombinemic dog blood added to suboptimal amounts of sodium oxalate failed to clot in most instances except in Tube 1, where the mean clotting time was 8.5 minutes.

Hypoprothrombinemic dog blood added to suboptimal amounts of equal parts of sodium citrate and sodium oxalate yielded mean clotting times of 7.8 minutes in Tube 1, 9.3 minutes in Tube 2, 10.1 minutes in Tube 3, and 11.9 minutes in Tube 4. In Tube 5 the clotting times averaged 16.6 minutes except for 1 specimen which remained fluid indefinitely.

Discussion. The mechanism of the anticoagulant action of oxalate or citrate has long been a controversial subject. The original concept by Arthus and Pages[1], Pekelharing[6], Morawitz[5], and others was based upon the hypothesis that calcium combines with oxalate or citrate, respectively, thus depriving the blood of a constituent, namely, calcium, considered indispensable for the formation of thrombin. It was ionized calcium in particular which was believed to be affected by the addition of oxalate or citrate.

In recent years, this interpretation has been subjected to criticism. It has been shown that protein bound calcium plays a more important part in the interaction with prothrombin than does ionized calcium[8]. Furthermore, the amount of oxalate or citrate sufficient to tie up the total calcium content of the blood does not prevent coagulation. A 3-fold amount of oxalate or citrate is required to achieve fluidity of the blood. The actual anticoagulant mechanism of citrate and oxalate therefore remains problematic.

Quick and Stefanini[9] suggested that prothrombin may combine with citrate as shown in their experiments with tricalcium phosphate in which prothrombin was not adsorbed from citrated plasma, possibly due to the formation of a prothrombin–citrate compound. If this is true, a given suboptimal amount of citrate which is insufficient to prevent coagulation of normal blood because it does not tie up all the prothrombin would delay coagulation

more in hypoprothrombinemia than in euprothrombinemia. This has been shown in the present study. The delay of coagulation with suboptimal amounts of sodium citrate has been such that even in moderate hypoprothrombinemia a 10 to 20-fold increase or more of the clotting times occurred. In these instances the corresponding prothrombin time was kept at a level varying around 20 seconds. When in a few instances anticoagulant therapy was intensified and the prothrombin time was prolonged to about 25 seconds, coagulation was suspended in all tubes except those containing 0.2 cc. of 0.01 molar sodium citrate.

This phenomenon was more marked when oxalate was used as the *in vitro* anticoagulant, but followed a more irregular pattern and was more unrelated to the prothrombin level. A comparison between the corresponding clotting times obtained with identical suboptimal amounts of oxalate and citrate leads to the obvious conclusion that their anticoagulant mechanism must be different. Many specimens of normal blood did not clot at all with the same amount of oxalate which, if substituted by citrate, led to a definite and measurable clotting time within about 60 minutes. In hypoprothrombinemia the results obtained with suboptimal amounts of sodium oxalate showed that coagulation was suspended to a greater degree than with sodium citrate, so that all specimens remained fluid except those containing 0.2 cc. and a few containing 0.1 cc. of 0.01 molar solution of sodium oxalate.

Further proof that the anticoagulant action of oxalate is different from that of citrate was obtained by experiments with a mixture of equal parts of 0.01 molar solution of sodium oxalate and sodium citrate. Whereas corresponding concentrations of sodium citrate alone or sodium oxalate alone resulted in delayed or even suspended coagulation as with oxalate, the mixture of both caused rather rapid clotting, so that the mean clotting time of 1 cc. of normal human blood added to 0.5 cc. of the mixture was only 13.8 minutes as compared with 47.5 minutes for the same amount of sodium citrate and total suspension of coagulation in the case of oxalate. If we were to assume temporarily that oxalate and citrate have a synergistic anticoagulant action, the mixture should have resulted in clotting times anywhere between those obtained with sodium citrate and those obtained with sodium oxalate. From the present study it seems, however, that each of the 2 components of the mixture acts separately with little synergistic action, if at all.

In hypoprothrombinemia the clotting times after addition of suboptimal amounts of the mixture of sodium oxalate and sodium citrate are prolonged, yet definitely measurable, and are shorter than those obtained with either citrate or oxalate. This again may be interpreted as lack of synergism of citrate and oxalate.

Additional support of the assumption that prothrombin combines with citrate was obtained in a comparison of the clotting times of human and dog blood. Whereas the addition of 0.48 cc. of 0.01 molar sodium citrate results in a mean clotting time of 37.2 minutes for human blood, a similar mean clotting time of 35.6 minutes was obtained in dogs after addition of 0.7 cc. of 0.01 molar sodium citrate. It can be concluded, therefore, that a larger amount of citrate is necessary to obtain the same clotting time with dog blood because its prothrombin content is considerably higher than in human blood.

Two other methods of detecting hypoprothrombinemia besides the prothrombin determination proper have been described. These are the "silicone

clotting time"[4] and the "heparin clotting time"[9], or the "sensitized clotting time"[2]. A basic difference between the results obtained by the determination of the silicone clotting time and those by the addition of suboptimal amounts of sodium citrate, in particular, is the fact that with the latter procedure a prolonged clotting time seems to be synchronous with the prolonged prothrombin time, whereas the silicone clotting time seems to be asynchronous with the prothrombin time.

The principle of the heparin clotting time, on the other hand, seems to be unrelated to the mechanism postulated in this study, namely, the union between prothrombin and citrate.

Further investigation as to the practical application of the results obtained in the above study is in progress.

Summary. 1. Addition of suboptimal amounts of sodium citrate to normal human and dog blood produces clotting times characteristic of the species and determined by the amount of anticoagulant solution.

2. Addition of suboptimal amounts of sodium citrate to hypoprothrombinemic human and dog blood yields markedly prolonged clotting times varying synchronously with the respective prothrombin level.

3. The parallelism of the prothrombin level and the amount of sodium citrate necessary to prevent or delay coagulation of blood supports the hypothesis previously advanced by others that sodium citrate unites with prothrombin.

4. Addition of suboptimal amounts of sodium oxalate to hypoprothrombinemic human and dog blood does not furnish notably different results as compared to those obtained with normal human and dog blood.

5. Addition of suboptimal amounts of a mixture of equal parts of sodium citrate and sodium oxalate to hypoprothrombinemic human and dog blood yields moderately prolonged clotting times as compared to those obtained with normal blood.

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SULFAGUANIDINE ABSORPTION AND EXCRETION FOLLOWING LOW ORAL MAINTENANCE DOSES IN MAN*

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THE present consensus regarding sulfaguanidine is that the drug is poorly absorbed from the intestinal tract. However, there is some evidence that the low levels of sulfaguanidine in the blood usually attained may be due, not to a low absorption rate, but rather to rapid urinary excretion[2]. Marshall's[5] early experience with this drug indicated that "sulfaguanidine is absorbed to a large extent when very small doses are given." On the usual maintenance dose of sulfaguanidine, blood levels are reached averaging about 2 mg. per 100 cc. Occasionally higher levels are encountered. The majority of the cases of Kirsner *et al.*[4] suggest that in the presence of ulcerative colitis, absorption may be markedly increased and higher blood sulfaguanidine levels may occur.

The question has arisen regarding the actual amount of sulfaguanidine absorbed from low oral maintenance dosage. To answer this question, 12 healthy young men were given low dosage of sulfaguanidine at 4-hour intervals for 6 days. Daily sulfaguanidine blood levels were determined, as was also the 24-hour urinary excretion on the 4th day.

Details of Method. Capsules of sulfaguanidine, U. S. P. (micro crystals), were prepared and supplied to each of the 12 subjects, 6 receiving those of 0.25 gm. size (approximately 3.4 mg./Kg. of body weight), and 6 receiving capsules of 0.38 gm. (approximately 5 mg./Kg.). Subjects were instructed to take one capsule by mouth every 4 hours; (5 times daily, at 6 and 10 a.m.; 2, 6, and 10 p.m.). Blood specimens for sulfaguanidine-level determinations were taken daily at 1:00 p.m. for 6 days, and again on the 8th day, 50 hours after the last dose of the drug. The chemical method employed in determining sulfaguanidine levels was that of Bratton and Marshall[1,6] with the use of the Klett-Summerson photoelectric colorimeter. Twenty-four hour urine specimens were collected from 6 a.m. of the 4th day to 6 a.m. the 5th day, for estimation of free and total urinary excretion of sulfaguanidine.

Results. In Table 1 the sulfaguanidine blood levels are recorded, and in Fig. 1 they are presented in graphic form. It will be noted that the 6 subjects on the lower dosage attained an average blood sulfaguanidine of 0.7 mg. per 100 cc. (free) and 1.07 mg. per 100 cc. (total). The subjects taking the higher maintenance dosage of 0.38 gm. attained an average blood level of 0.85 mg. (free) and of 1.26 mg. (total) of sulfaguanidine per 100 cc. After the 1st day, the average levels remained quite uniform throughout the period of administration.

The urinary excretion, detailed in Table 2, averaged the same for both dosage groups. 69% of the 24-hour intake (with individual variations ranging from 47% to 107%).

A rearrangement of these subjects into groups in the order of their fluid output (Table 3) shows a correlation between fluid output and the total amount of drug excreted.

Discussion. A summary of 4 previous reports (Table 4) in which the custom-

* This study was aided by a grant from Special Milk Products, Inc., Los Angeles, California.

ary sulfaguanidine dosage was used, (approximating 50 mg./Kg. of body weight, at 4-hour intervals) reveals an average blood level of free sulfaguanidine of 2.01 mg. per 100 cc. Comparing this with the results of the present study, it is apparent that with this small dosage approximating 1/10th the usual amount (5 mg./Kg.) an average blood level was attained (0.85 mg. per 100 cc.) which was 40% of the free sulfaguanidine level produced by a maintenance dose 10 times as high. It is further apparent that by increasing the

TABLE 1.—DAILY SULFAGUANIDINE BLOOD LEVELS (MG. PER 100 CC.)

Dosage	*Subject*	*Wt. (Kg.)*		*Days* 1	2	3	4	5	6	8
.38 gm. (Approx. 5 mg./Kg.)	A-1	87.75	F.	.79	.71	.92	.72	.88	.73	.27
			T.	.79	.77	1.49	1.10	1.41	1.13	.41
	A-2	80.85	F.	.61	.75	1.00	.54	.81	.95	.37
			T.	.70	1.63	1.00	.74	1.60	1.69	.48
	A-3	74.7	F.	.54	1.21	1.06	1.06	.70	.95	.41
			T.	.68	1.25	2.18	1.40	.80	1.67	.44
	A-4	75.4	F.	.50	.50	.47	.74	.63	.41	.28
			T.	.66	1.08	.80	1.13	.87	.99	.39
	A-5	75.85	F.	.61	1.13	1.35	1.26	.88	.82	.39
			T.	.93	1.19	1.98	1.60	1.50	1.65	.43
	A-6	76.65	F.	1.11	1.13	1.04	.88	.88	1.18	.39
			T.	1.22	1.19	1.63	1.74	1.74	1.48	.39
	Ave.	78.53Kg.	F.	.69	.91	.97	.87	.80	.84	.36
			T.	.83	1.19	1.51	1.29	1.32	1.44	.42

Total ave., days 1 to 6, Free, .85 mg./100 cc.
Total, 1.26

Dosage	*Subject*	*Wt. (Kg.)*		*Days* 1	2	3	4	5	6	8
.25 gm. (Approx. 3.4 mg./Kg.)	B-1	78.5	F.	.61	.69	.90	.79	.54	.64	.46
			T.	.79	1.86	.91	1.23	.97	1.03	.53
	B-2	78.65	F.	.54	.65		.63	.81	.45	.28
			T.	.99	.79		1.23	.85	.59	.30
	B-3	77.7	F.	.61	.61	.55	.54	.63	.55	.28
			T.	.63	.64	.63	1.42	.90	1.27	.28
	B-4	62.9	F.	.47	.75	.74	.65	.63	.34	.32
			T.	.56	.81	1.71	1.00	1.14	.85	.39
	B-5	64.3	F.		1.07		1.23	.86	.83	.19
			T.		1.80		1.69	1.36	1.48	.64
	B-6	81.4	F.	.48	.67	1.14	.67	.77	1.02	.26
			T.	.52	1.03	1.32	1.35	1.12	1.15	.27
	Ave.	73.91Kg.	F.	.54	.74	.83	.75	.71	.64	.30
			T.	.70	1.16	1.14	1.32	1.06	1.06	.40

Total ave., days 1 to 6, Free, .70 mg./100 cc.
Total, 1.07

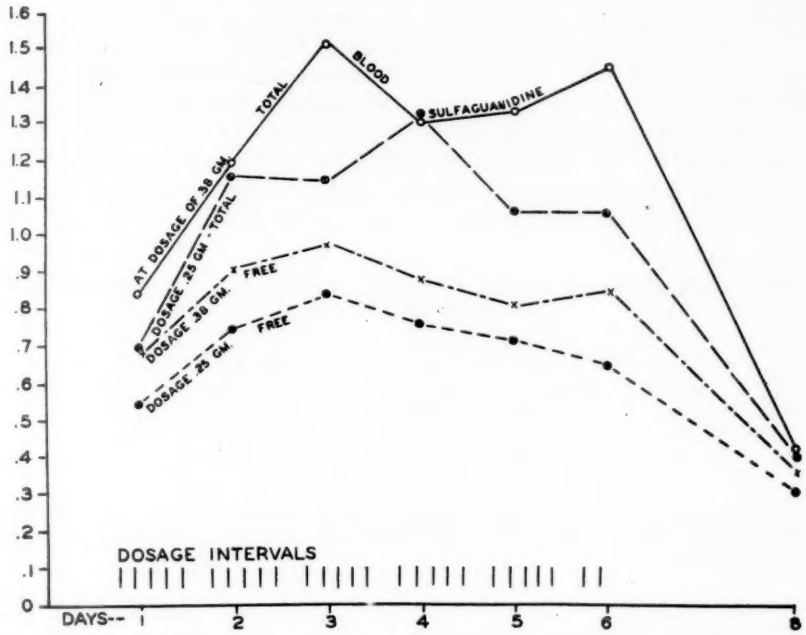

FIG. 1.—Daily average free and total sulfaguanidine blood levels resulting from maintenance doses of 0.25 gm. and 0.38 gm. at 4-hour intervals. Abscissae, mg. per 100 cc.

TABLE 2.—24-HOUR URINARY EXCRETION OF SULFAGUANIDINE

			Free Sulfaguanidine			*Total Sulfaguanidine*		
	Subject	*24-hr. Urine, vol.*	*mg./100 cc.*	*24-hr. Excretion*	*% of Total*	*mg./100 cc.*	*24-hr. Excretion*	*% of 24-hr. Intake*
Dosage .38 gm.	A-1	2565 cc.	26	0.66 gm.	55	47	1.19 gm.	63
	A-2	700	85	0.60	61	140	.98	52
	A-3	3500	28	0.96	47	58	2.04	107
	A-4	1215	47	0.58	65	73	.88	47
	A-5	820	98	0.81	62	159	1.30	69
	A-6	1415	56	0.79	53	105	1.48	78
	AVE.	1703 cc.	57 mg./100 cc.	0.73 gm.	56%	97 mg./100 cc.	1.31 gm.	69%
Dosage .25 gm.	B-1	1000 cc.	41	.41 gm.	65	63	.63 gm.	50
	B-2	1420	32	.46	52	62	.89	71
	B-3	1700	40	.68	76	50	.86	68
	B-4	1500	30	.46	55	55	.83	66
	B-5	1460	72	1.05	78	92	1.34	107
	B-6	905	43	.39	58	74	.67	53
	AVE.	1331 cc.	43 mg./100 cc.	.57 gm.	66%	66 mg./100 cc.	.87 gm.	69%
	A & B AVE.	1517 cc.	50 mg./100 cc.	.65 gm.	60%	81.5 mg./100 cc.	1.09 gm.	69%

dosage by 50%, from our low figure of 3.4 mg./Kg., to 5 mg./Kg., we obtained an increase of free sulfaguanidine in the blood of only 20% (from 0.70 to .85 mg./100 cc.).

The 4 subjects with the lowest fluid output, averaging 856 cc., excreted 56% of their 24-hour sulfaguanidine intake. The 2nd group of 6 subjects, with an output averaging 1451 cc., excreted 72.8% of the day's intake. In the 3rd group, there were but 2 subjects whose total fluid output, averaging 3033. cc., accounted for 84.7% of the day's intake of sulfaguanidine. Although the 3rd group with highest fluid output is too small to be significant, yet the general trend is apparent: The greater sulfaguanidine excretion accompanies the greater fluid output. The relatively high urinary excretion figures here reported add confirmatory evidence to the ease of absorption of sulfaguanidine in low dosage from the small intestine.

Summary and Conclusions. 1. Lower oral maintenance dosage of sulfaguanidine in the range of approximately 5 mg./Kg. in humans is accompanied by a relatively higher level of sulfaguanidine in the blood.

2. In 12 subjects on low oral maintenance dosage, the 24-hour urinary excretion of sulfaguanidine averaged 69% of the day's intake of the drug, a higher excretion rate accompanying an increase in fluid output. Approximately 3/5ths of the sulfaguanidine in the urine appeared in the free form.

3. Sulfaguanidine in low oral dosage is readily absorbed from the intestinal tract.

TABLE 3.—RELATION OF TOTAL FLUID OUTPUT TO URINARY EXCRETION OF SULFAGUANIDINE

No. of Subjects	*Total Fluid Output*		*Sulfaguanidine in Urine (as % of 24-hr. Intake)*
	Range, cc.	*Ave., cc.*	
4	700–1200	856	56.0
6	1200–1700	1451	72.8
2	Over 1700	3033	84.7

TABLE 4.—SULFAGUANIDINE BLOOD LEVELS RESULTING FROM USUAL DOSAGE (SUMMARIZED FROM PREVIOUS REPORTS OF OTHER AUTHORS) COMPARED WITH PRESENT STUDY

Author	*Subjects*	*Dosage*	*Ave. Free-Sulfaguanidine Blood Level*
Marshall, *et al.*[6]	4 children	50 mg./Kg. q. 4 hr. or 100 mg./q. 8 hr.	2.27 mg./100 cc.
Stanier & Stapleton[8]	5 children	50 mg./Kg. q. 4 hr.	1.56
L. C. Hall[3]	15 children with bac. dysentery	Initial, 100 mg./Kg. Maintenance, 50 mg./Kg. q. 4 hr.	2.3
S. G. Page[7]	11 young adults with bac. dysentery	Initial 7. gm. Maintenance 3.5 gm. q. 4 hr. for 48 hrs. Then 3.5 gm. q. 8 hr.	1.9 (3rd day)
		Ave.	2.01 mg./100 cc.
Present Study	6 adults	5 mg./Kg. q. 4 hr.	.85 mg./100 cc.
	6 adults	3.4 mg./Kg. q. 4 hr.	.70 mg./100 cc.

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HYPERGLYCEMIA AND GLYCOSURIA IN THE CHRONIC ALCOHOLIC WITH HEPATIC INSUFFICIENCY. CLINICAL OBSERVATIONS IN 10 PATIENTS

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Clinical studies have suggested that liver abnormalities may cause hyperglycemia and glycosuria and stress the need for early recognition and proper treatment of hepatogenic diabetes[19]. This thesis is supported by observation of transient hyperglycemia in patients with fatty livers, hepatitis, and infections of the biliary tree[15,18,20,28]. Ten patients with hyperglycemia and glycosuria appearing after prolonged periods of marked alcoholism and poor nutrition have been studied in evaluating this problem.

Material and Methods. The patients were from 35 to 71 years of age. All were males with histories of marked degrees of alcoholism and poor diets for 5 to 40 years before discovery of the carbohydrate disturbance. Nine had polyuria and polydipsia, in 1 a routine blood sugar test and urinalysis revealed hyperglycemia and glycosuria. Eight had a previous diagnosis of diabetes mellitus and had taken insulin for short periods. One patient was treated for portal cirrhosis 12 months before the onset of a diabetic syndrome, at which time he had a normal blood sugar.

A series of biochemical liver function tests were employed and consisted of serum bilirubin[21], urinary bile[11], urinary urobilinogen[29], serum alkaline phosphatase[2], bromsulfalein excretion[22], serum albumin and globulin[3], cephalin–cholesterol flocculation[13], thymol turbidity[23], total serum cholesterol and cholesterol esters[1], and prothrombin time[25].

Serum bilirubin levels above 1.0 mg. per 100 cc., serum alkaline phosphatase of more than 5 Bodansky units, and retention of 5.0% or more of bromsulfalein at 45 minutes (employing 5 mg. per Kg. of body weight) were considered abnormal. Likewise, total serum proteins less than 6.5 gm. per 100 cc. or reversal of the serum albumin–globulin ratio, 3 to 4 plus cephalin–cholesterol flocculation at 48 hours, and thymol turbidity values in excess of 4 units at 30 minutes were considered abnormal. Normal total cholesterol standards ranged between 190 and 250 mg. per 100 cc. with esters constituting 60 to 80% of the total cholesterol. Normal prothrombin time was within 1 second of the control value.

Intravenous glucose tolerance tests[17], using 0.5 gm. of glucose per Kg. of body weight, were performed in the fasting state after the patient had been on a carbohydrate intake of 300 gm. a day for 3 days. In 6 patients this test was performed prior to therapy and repeated serially. The serum inorganic phosphoros[4] was determined along with each blood sugar determination during the course of the glucose tolerance test. Intravenous galactose tolerance tests were performed using 0.5 gm. of galactose per Kg. of body weight[6]. The epinephrin test[16,27] for appraisal of glycogen storage was performed, using 0.01 cc. of a 1:1000 solution of epinephrin per Kg. of body weight. Blood sugars were determined by the method of

Folin and Wu on venous blood. Special studies included serum amylase[14], insulin tolerance[9], phenosulfonphthalein excretion[5], 17-ketosteroid excretion[10], roentgenograms of extremities for calcification of vessels, and basal metabolism.

Needle biopsy of the liver was performed with the "Vim" Silverman needle without complications[30] and sections stained with hematoxylin and eosin. A diagnosis of fatty liver, without fibrosis, was made in the presence of fat globules occupying 20% or more of the biopsy section. A diagnosis of portal cirrhosis (diffuse fibrosis) was made in the presence of periportal fibrosis, pseudolobulation, and bile duct proliferation with or without hyaline necrosis and fatty or lymphocytic infiltration.

Hepatotherapy consisted of bed rest with a weighed diet of 350 gm. of carbohydrate, 125 gm. of protein, and 80 gm. of fat, plus daily divided doses of 6 gm. each of methionine and choline and 3 therapeutic multivitamins containing a total of 75,000 units of Vitamin A, 3,000 units of Vitamin D, 30 mg. of thiamine hydrochloride, 15 mg. of riboflavin, 450 mg. of niacin, and 450 mg. of ascorbic acid. The results of therapy were assayed by serial blood and urinary sugar determinations, repeated liver function studies, and needle biopsy.

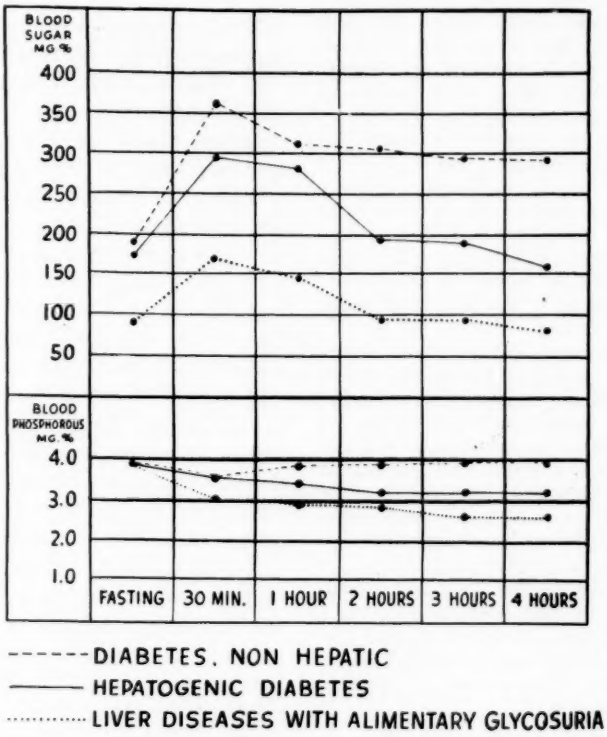

Fig. 1—Composite glucose tolerance curves with simultaneous inorganic phosphate studies in Cases 1, 2, 7, 8, 9, 10. Glucose tolerances were not performed initially in patients with marked hyperglycemia.

Clinical Observations. Hepatomegaly, weight loss, glossitis, cheilitis, and paresthesias were present in each of the patients before treatment. Jaundice was present in 4 patients, splenomegaly in 4, spider angiomata in 3, peripheral neuropathy in 2, esophageal varices in 1, and ascites and ankle edema in 1.

Liver function studies before therapy showed abnormal bromsulfalein retention and disturbed protein fractions in each of the patients. Cephalin flocculation and chol-

esterol partitions were abnormal in 8 patients, hyperbilirubinemia was present in 5, and prothrombin time was abnormal in 2. Alkaline phosphatase was elevated in 1 patient and thymol turbidity was abnormal in 3 patients.

Intravenous glucose tolerance curves showed a tendency to return to the fasting level in 3 hours. A composite curve of the 6 patients with pre-therapy glucose tolerance showed levels intermediate between those observed in non-hepatic diabetes and liver disease associated with alimentary glycosuria (Fig. 1). Simultaneous serum inorganic phosphoros determinations showed decreases in the phosphoros level but with less depression than that observed in liver disease associated with alimentary glycosuria (Fig. 1). Epinephrin studies revealed variable increases in blood sugar after the injection of epinephrin (Table 3). Galactose tolerance tests showed abnormal curves in 4 patients. Serum amylases, basal metabolic studies, and 17-ketosteroid excretion were normal in each instance. Pre-therapy histologic studies revealed fatty liver in 3 instances and portal cirrhosis in 7 instances.

None of the group had a history of clinical acidosis despite periods of scanty food intake associated with heavy consumption of alcohol varying from 2 weeks to 2 months. No patient had hypertension or clinical evidence of peripheral vascular disease. Retinal studies revealed A-V nicking and increased arterial reflexes in 4 patients. None had retinal hemorrhages and exudates or aneurysmal dilatation of retinal venules. Roentgenograms of the soft tissues revealed no changes in 4 and moderate calcification of peripheral arteries in 4. Renal function studies revealed normal PSP excretion in 7 patients and impaired excretion in 3 patients. Cataracts were not present in any of the patients.

Results of Therapy. During hospitalization carbohydrate tolerance returned to normal in 8 patients. In 2 patients previously observed with hyperglycemia disappearing with hepatotherapy, 120 units of insulin daily did not affect hyperglycemia and glycosuria. The hospital period ranged from 4 to 12 weeks with an average of 8 weeks per patient.

Along with improvement of carbohydrate tolerance, diabetic symptoms, neuropathy, edema, and jaundice disappeared if they had been present; hepatomegaly decreased; and biochemical liver function studies returned toward normal (Table 1). There was an improvement in sense of well being, and an average weight gain of 4.1 Kg. per patient. Bromsulfalein, serum bilirubin, and cephalin–cholesterol flocculation returned to normal in each instance. With improved liver function tests, needle biopsies were repeated. Fibrosis, bile duct proliferation, and pseudolobulation remained essentially unchanged in post-therapy biopsies. Pleomorphism and cellular infiltration decreased and fat disappeared (Table 2). Hyaline necrosis noted in 2 sections was not demonstrated in repeat biopsies.

After the hepatic disease was felt to be controlled, patients were discharged to the Liver Clinic on the same regimen they had received during their hospital stay. Four patients attended the clinic regularly and adhered to their prescribed regimen (Group I); the other 6 resumed their alcoholic pattern (Group II). In Group I, consisting of 2 patients with fatty livers and 2 with cirrhosis, further clinical, biochemical, and histologic improvement occurred. With intercurrent illness serial blood sugar studies revealed normal glucose tolerance in 3 patients and slight changes in glucose tolerance in 1 patient. The patients with fatty livers became asymptomatic. Those with portal cirrhosis maintained symptoms and signs of their cirrhotic process.

Despite intensive psychotherapy and medical supervision, after discharge the 6 patients in Group II resumed their alcoholism and poor diet intake. Two of this group constantly denied alcoholic intake, although members of their family stated they periodically became intoxicated. Four patients freely admitted consuming whiskey. Serial carbohydrate tolerance studies revealed maintenance of normal sugar metabolism in 1 patient despite alcoholism, and varying degrees of hyperglycemia and glycosuria in 5 patients.

TABLE 1.—INITIAL BIOCHEMICAL THERAPEUTIC RESPONSE OF 10 PATIENTS

Case		Fasting Blood Sugar	Period Treated	Urine Sugar in 2½ hr.	BSP % Retained	Serum Bil. mg./100 cc.	Ceph. Floccu-lation	Serum Alb. gm./100 cc.	Serum Glob. gm./100 cc.	Serum Chol. mg./100 cc.	Serum Chol. Esters mg./100 cc.
1. C. M.	B	190	8 wk.	21.5	20	0.7	4+	2.84	4.66	362	158
	A	110		0	9	0.0	1+	3.45	3.74	239	100
2. J. H.	B	180	10 wk.	12	28	1.6	3+	3.45	4.0	206	130
	A	110		0	11	0.8	1+	3.65	4.1	291	145
3. J. S.	B	310	5 wk.	10	10	0.8	2+	3.64	3.16	383	191
	A	130		0	0	0.3	0	4.41	2.39	308	181
4. W. S.	B	460	12 wk.	24	0	11.5	2+	2.31	3.49	188	109
	A	90		0	0	0.1	0	4.30	3.45	210	150
5. P. S.	B	270	12 wk.	19	14.5	1.0	3+	3.18	4.32	123	77
	A	180		5	0	0.5	1+	4.0	4.2	229	109
6. PeS.	B	250	12 wk.	12	20	2.5	4+	3.9	2.8	180	90
	A	140		6	2	1.0	1+	4.2	2.7	210	135
7. W. S.	B	220	8 wk.	14	30	3.4	4+	4.06	3.74	291	207
	A	105		0	4	0.7	0	4.05	3.8	230	140
8. F. B.	B	160	6 wk.	18	12.5	1.2	4+	2.84	4.66	325	213
	A	120		0	6	0.3	0	4.0	3.5	271	158
9. F. F.	B	172	4 wk.	8	12	0.5	2+	3.27	2.93	717	365
	A	86		0	0	0.1	0	3.55	3.25	234	126
10. G. W.	B	184	4 wk.	15	20	0.1	2+	3.36	4.84	657	358
	A	99		1	0	0.1	0	4.2	3.1	320	180

B—Before Therapy
A—After Therapy
BSP—Bromsulfalein

TABLE 2.—HISTOLOGICAL CHANGES WITH THERAPY IN 10 PATIENTS

Case	Period Between Biopsies		Fibrosis	Fat Infiltration	Pleomorphism	Bile Duct Proliferation	Pseudolobulations	Infiltration	
								Lymphs	Polys
1. C. M.	8 wk.	B	3+	2+	2+	2+	3+	2+	1+
		A	3+	0	1+	2+	3+	2+	1+
2. J. H.	10 wk.	B	2+	0	1+	2+	2+	1+	0
		A	1+	0	1+	1+	2+	0	0
3. J. S.	5 wk.	B	0	2+	1+	0	0	0	0
		A	0	0	0		0	0	0
4. W. So.	12 wk.	B	2+	3+	3+	1+	1+	2+	1+
		A	2+	0	2+	1+	1+	1+	0
5. PaS.	12 wk.	B	3+	0	3+	2+	4+	2+	1+
		A	3+	0	2+	2+	4+	2+	1+
6. PeS.	12 wk.	B	4+	3+	3+	2+	4+	3+	1+
		A	4+	0	2+	2+	4+	2+	1+
7. W. S.	8 wk.	B	1+	2+	2+	0	0	0	0
		A	1+	0	1+	0	0	0	0
8. F. B.	6 wk.	B	2+	2+	1+	1+	1+	1+	1+
		A	0	1+	1+	1+	1+	1+	0
9. F. F.	4 wk.	B	0	2+	1+	0	0	0	0
		A	0	0	0	0	0	0	0
10. G. W.	4 wk.	B	0	3+	1+	0	0	0	0
		A	0	0	0	0	0	0	0

B—Before Therapy
A—After Therapy

ETIOLOGICAL CONSIDERATIONS. In each of the patients an effort was made to eliminate the possibility that a toxic or nutritional factor leading to hepatic injury also may have produced a pancreatic or other endocrine lesion, with correction of insulin insufficiency by removal of the noxious agent. Studies of serum amylase, basal metabolism, and 17-ketosteroid excretion showed no abnormalities.

Liver disease could produce hyperglycemia and glycosuria by interfering with hepatic hemostasis of blood sugar (glycogenesis and glycogenolysis) or by unmasking a relative insulin insufficiency. Results of therapy suggest that 4 patients had no insulin insufficiency, the carbohydrate disturbance being directly related to the liver injury. Three of these patients were in Group I and 1 was in Group II. Intercurrent illness such as viral respiratory infections had no effect on carbohydrate tolerance. The following case history is illustrative:

Case Reports. CASE 2. J. H., 70, a retired bartender, was first seen in the outpatient department because of urinary frequency. He had eaten poorly and consumed 2 to 3 pints of whiskey daily and occasional wine and beer for 30 years. A blood sugar determination showed 285 mg. per 100 cc. and urinalysis showed a 3% glycosuria. He was given a diet of 160 gm. of carbohydrate, 80 gm. of protein, and 80 gm. of fat, with 15 units of crystalline insulin each day. He improved and his blood sugar decreased to 180 mg. per 100 cc. He was hospitalized because of the appearance of ankle edema and ascites, associated with hepatomegaly, splenomegaly, and jaundice. Liver function studies revealed a 4+ cephalin flocculation, hyperglobulinemia, bromsulfalein retention, hyperbilirubinemia, and a sugar rise of 20 mg. per 100 cc. with the glycogen storage test. Needle biopsy of the liver showed portal cirrhosis with cellular infiltration. Serum amylase, BMR, 17-ketosteroid excretion, and BSP (bromsulfalein) excretion were all normal. Insulin was discontinued and the patient was placed on the hepatic regimen. On this therapy, carbohydrate tolerance returned to normal. Liver functions and a repeat liver biopsy showed improvement (Tables 1 and 2). He was discharged to the out-patient department after a 10-week period. Serial observations at 6-month intervals revealed a decrease in liver size, reduction in ascites, maintenance of normal carbohydrate metabolism with normal glucose tolerance, good glycogen storage, and impaired galactose tolerance. Liver function study 3 years after initial observation revealed continued abnormal function with retention of 20.5% bromsulfalein, serum albumin 3.55 gm. per 100 cc., serum globulin 3.75 gm. per 100 cc., cholesterol 246 mg. per 100 cc., cholesterol esters 130 mg. per 100 cc. Neither a urinary tract infection nor viral respiratory infection had any influence on the patient's carbohydrate tolerance.

Four patients were felt to have a relative insulin insufficiency made overt by liver disease, as hyperglycemia often developed after minor hepatic changes and disappeared with short-term hepatotherapy, although the basic liver pathology remained. The following case history is illustrative.

CASE 3. J. S., a 59-year old fireman, was hospitalized for delirium tremens. He had a history of alcoholism and poor dietary habits for a period of 40 years. He was found to have hepatomegaly and hyperglycemia, both of which disappeared with rest and a general diet. One year later he was readmitted in delirium tremens. He had hyperglycemia, hepatomegaly, and abnormal liver function studies, all of which persisted on a general diet. A needle biopsy revealed a moderately fatty liver. He was given the hepatic regimen and within 5 weeks his carbohydrate tolerance, liver function and liver biopsy were normal (Tables 1 and 2). Serial follow-up revealed normal carbohydrate tolerance except for periods of febrile respiratory infections. Three years after initial observation he resumed his alcoholic consumption for several weeks. Hyperglycemia and glycosuria appeared and liver function tests showed a hyperglobulinemia and bromsulfalein retention. A liver biopsy showed lymphocytic infiltration. Pancreatic function studies were normal. With rest and the hepatic regimen his carbohydrate studies again returned to normal.

Two patients followed over an 8-year period developed irreversible insulin insufficiency. The mechanism of their hyperglycemia is obscure, although its

relationship to liver disease seems obvious. The following case history is illustrative.

CASE 6. P. S., a 50-year old truck driver, was hospitalized in 1942 with glossitis, hepatomegaly, and undernutrition. His past history revealed poor dietary habits with daily consumption of 1 to 2 pints of whiskey for several years. A fasting blood sugar was 154 mg. per 100 cc., urine sugar was 1+, and a glucose tolerance curve was diabetic. On a diet of 200 gm. of carbohydrate, 100 gm. of protein and 90 gm. of fat daily, he became aglycosuric without insulin. After discharge from the hospital he returned to alcoholism. He was seen again in 1946, at which time he was jaundiced and had an enlarged liver and glossitis. Fasting blood sugar levels fluctuated above 200 mg. per 100 cc. and there was a persistent 4+ glycosuria. He was given a hepatic regimen and insulin with improvement of his hepatic status. Over a 3-month period his carbohydrate tolerance returned to normal. He resumed his alcoholic habits and was rehospitalized in 1947 with hepatomegaly, jaundice, hyperglycemia, and glycosuria. His carbohydrate tolerance again became normal with hepatic therpy. In 1948, after a 7-month period of alcoholism, he was rehospitalized with hepatomegaly, splenomegaly, jaundice, and esophageal varices. Liver function studies revealed marked changes (Table 1). A needle biopsy showed portal cirrhosis with fat. Despite prolonged therapy, during which time there was a marked improvement in liver function and a mobilization of fat from the liver, carbohydrate intolerance remained. Ninety units of insulin had little effect on hyperglycemia and glycosuria. In 1949, 1950, and 1951, after periods of continued drinking and poor dietary intake, hepatotherapy failed to improve his carbohydrate tolerance and progressive signs and symptoms of hepatic insufficiency have been noted.

The major diagnostic problem has arisen in differentiating patients with hepatogenic diabetes from those with diabetes mellitus and secondary liver disease. Given a patient with hyperglycemia and liver dysfunction, hepatic steatosis, or fibrosis, it would be valuable to have a simple device to decide which is primary. In our experience glucose tolerance tests with simultaneous inorganic phosphorous determinations do not permit this differentiation, as patients with familial diabetes and secondary toxic cirrhosis have very similar patterns[20]. Similarly, histological glycogen content of liver biopsies, protein and cholesterol studies, and galactose tolerance and epinephrin tests have not helped. It is suggested that the following criteria be used for a diagnosis of hepatogenic diabetes: 1) a history of exposure to hepatotoxins or liver injury prior to the appearance of the diabetic syndrome; 2) physical and biochemical, or histologic (or both) evidence of liver disease; 3) no familial history of diabetes or history or clinical evidence of pancreatic, pituitary, adrenal, or thyroid disease; 4) disappearance of hyperglycemia and glycosuria on hepatic therapy without insulin.

Comment: Hyperglycemia and glycosuria co-exist with liver disease in a large number of patients: a) well-controlled diabetes is associated with liver dysfunction and fatty changes of the liver in some patients[32]. b) Poorly controlled diabetes and that associated with complicating disease processes is associated with a high incidence of liver dysfunction and histological changes[8,12,19]. c) The diabetic develops his share of liver changes due to congestive heart failure[31], malignancy, viral hepatitis, and biliary obstruction or infection. d) Occasionally, pancreatitis is associated with liver injury and hyperglycemia and glycosuria[26]. e) Hemochromatosis causes liver and pancreatic lesions, both of which may contribute to hyperglycemia. f) Acute hepatic injury or subclinical liver damage due to infection or obesity may cause transient hyperglycemia and glycosuria[24]. To these may be added chronic hepatic disease as a cause of hyperglycemia and glycosuria.

A most remarkable clinical feature of this series of patients is their ability to consume large quantities of whiskey and eat poorly, not developing significant ketosis (although they receive

no insulin), despite maintained hyperglycemia and glycosuria. Most diabetics adhering to such a regimen rather readily develop ketosis and diabetic coma. A carbohydrate intake of 350 gm. without insulin led to improvement of liver dysfunction and improved carbohydrate tolerance. Similar therapeutic results have been noted with acute hepatic injuries associated with transient hyperglycemia and glycosuria.

TABLE 3.—AVERAGE MAXIMUM RISE OF BLOOD SUGAR ON GLYCOGEN STORAGE TEST

Condition	*No. of Patients*	*Average Blood Glucose Rise*
Diabetes Mellitus	10	90 mg.%
Hepatogenic Diabetes	10	20 mg.%
Normal Controls	20	50 mg.%
Severe Liver Disease without Carbohydrate Disturbance	25	15 mg.%

The incidence of vascular disease in this group requires further study. Evidence of coronary artery disease, hypertension, and renal vascular changes characterizing many diabetics was not present. In contrast, 4 patients with long-standing diabetes and the Kimmelstiel–Wilson syndrome have been observed with complicating fatty livers in 2 instances and portal cirrhosis in 2 instances.

In addition to providing a medium for further study of the etiology and effects of hyperglycemia and glycosuria, such patients offer the clinician an opportunity to recognize and simultaneously treat 2 related abnormalities. The effectiveness of therapy is dependent to a great extent on the ability of the patient to adhere to the prescribed regimen. The hepatic abnormality, if unrecognized and improperly treated, will become irreversible and may eventually produce sustained hyperglycemia; with early recognition and institution of proper therapy as soon as feasible, the hepatic changes and the hyperglycemia and glycosuria may be returned to normal.

Summary and Conclusions. 1. Ten patients have been observed with histories of chronic alcoholism and poor dietary habits prior to the appearance of a diabetic syndrome, where hepatic therapy without insulin caused improvement in the hepatic status and disappearance of the hyperglycemia and glycosuria. None of the patients had familial diabetes or evidence of pancreatic, pituitary, adrenal, or thyroid disease.

2. Therapeutic responses suggested liver disease produced hyperglycemia by interfering with hepatic homeostasis of blood sugar in 4 patients and by the unmasking of a relative insulin insufficiency in 4 patients. The mechanism was obscure in 2 patients developing insulin resistant diabetes.

3. Significant ketosis was not observed, although patients consumed large quantities of whiskey, ate poorly, and received no insulin. None of the patients had clinical evidence of accelerated degenerative vascular disease.

4. The differential diagnosis of diabetes with secondary liver changes and hepatogenic diabetes is difficult and seems to be most readily made by prolonged therapeutic observation.

5. Prognosis for both the liver changes and the carbohydrate disturbances was good with proper treatment. Six patients returning to alcoholism and poor diets had varying degrees of relapse. Clinical abnormalities were readily controlled in 4 patients adhering to their therapeutic regimen.

The authors gratefully acknowledge the advice and assistance of Dr. Elmer L. Sevringhaus.

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HEPATIC FACTORS IN SALT AND WATER METABOLISM

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THAT the liver plays an important role in the regulation of electrolyte and water metabolism has been suspected for many decades. The literature of the late 19th century contains references to hepatogenous edema, and near the turn of the century French physicians were treating the ascites of cirrhosis empirically with low-salt diets. Within recent years attention has been refocused on water movements in both acute and chronic liver disease, and a flurry of publications appeared on a rather ephemeral entity called "liver death" or the hepatorenal syndrome. Recently quantitative definition of disturbances in the distribution and excretion of water and salt in clinical states of liver dysfunction has been accomplished, and the suggestion has been offered that endocrine influences, altered by the presence of hepatic disease, determine at least in part the renal excretion of water and salt in these states.

This paper will review rather briefly a few of the earlier important contributions to the problem, will describe the entities which some believed to represent the hepatorenal syndrome, and will present in moderate detail results of recent experiments centered upon the accumulation of fluid, salt and water excretion in the presence of liver disease, the demonstration of antidiuretic factors, and the presence of hepato-endocrine relationships which might influence the foregoing phenomena.

Early Evidence of Changes in Water Metabolism with Hepatic Disease. Pick[57], in a Harvey lecture, has summarized the older evidence concerning hepatic influences on water balance, emphasizing experiments employing the Eck-fistula dog. In the experiments of Lamson and Roca[44], which Pick cited, physiologic saline solution was injected parenterally, and diuresis was delayed as compared to that of normal dogs. However, the hepatic artery and portal vein had been ligated, so the preparation more closely resembled a hepatectomized one than

that which is generally understood to be an Eck fistula. On the other hand, in the true Eck-fistula dog it was found that water administered orally resulted in a more precipitous diuresis than that occurring in the unprepared animal. This type of experiment was interpreted as providing evidence for a "hydrodynamic" concentrative function of the liver. Enterogenous water, bypassing the liver through the Eck fistula, avoided concentration by that organ and was excreted more rapidly by the kidney, and, conversely, parenteral saline solution was more slowly excreted by the kidneys, because little of the fluid could pass through the liver. The logic of this thesis and its interpretation are not completely apparent, though in a later paper Pick[58] again called attention to the Eck-fistula experiments, citing them as evidence for an important hydrodynamic function of the liver and using the observations of Priestley[59] and Smirk[71] as evidence that the liver (with all the other tissues) was an important recipient of enterogenous water for storage before excretion. That the liver exerts such an influence seems probable, but its specificity and relative importance in the human animal appear to require further definition. An interesting series of experiments along this line could be constructed around patients before and after establishment of portacaval anastomoses for portal hypertension.

Others[28,29,58] have presented evidence for the existence of diuretic and antidiuretic liver hormones identified in alcoholic liver extracts, but more recently attention has been directed elsewhere. True, some investigators have reported mitigation of ascites and improvement of cirrhosis following administration of liver extracts, but interpretation has been toward improvement of liver function rather than toward activity of a specific hormone. Evidence for the existence of hepatogenous diuretic or antidiuretic humoral factors seems inconclusive.

Adlersberg[1] in a series of reports presented rather clear-cut evidence of changes in water tolerance in patients with liver disease. In dogs with livers damaged by phosphorus he demonstrated an early "shift to the left" or early diuresis (as compared to control levels), which was succeeded by diminished and delayed diuresis or a "shift to the right." This early diuresis is perhaps comparable to that obtained in the Eck-fistula dogs, though the underlying changes in hepatic vasculature are difficult to imagine; perhaps the acutely damaged liver is unable "hydrodynamically" to accommodate the water load, and the delay later in the experiment may be related to the type of altered homeostasis encountered in severe hepatitis and cirrhosis. Parenthetically, in the "reverse-Eck-fistula dog" (all the inferior caval blood is shunted through the liver) greatly delayed and reduced water diuresis results[42,52]. This procedure itself probably produces severe liver damage. Adlersberg and Fox[2], pursuing these leads, carried out careful clinical studies of patients with various types of hepatic disease and found changes which they considered to be highly significant: In contrast to results obtained for 30 healthy control subjects, patients with severe hepatitis, when subjected to water tolerance tests, exhibited decreased total elimination. The amount of decrease paralleled the clinical severity, and patients with mild hepatitis showed normal or increased elimination, though from the published data the significance of the latter observation is not completely evident. Data on the hourly rate of diuresis in normal men indicated a rise to a maximum during the second and third hours, followed by a decline. Patients with mild hepatitis showed

curves similar to those of normal men, though "not infrequently the rate was accelerated so that the maximum occurred in the first hour." In patients with severe hepatitis, delayed and incomplete diuresis was the rule. Water tolerance tests were normal in 10 patients with obstructive jaundice. This important series of observations demonstrated at least that, with severe parenchymal liver disease, delayed and incomplete water diuresis was frequently encountered.

Jones and Eaton[39], studying a group of patients with acute and subacute hepatitis by simple measurement of fluid intake and output, found rather consistently that conspicuous diuresis heralded clinical improvement. The degree of diuresis was variable, being greater when edema, ascites, or hydrothorax had been present, but it occurred even when no accumulation of fluid had been suspected. They concluded that as the status of the liver improved, fluid was shifted from the tissues to the blood with resultant diuresis. Thus, before studies of sodium excretion and antidiuretic factors had been made in the presence of liver disease, delayed excretion of water and spontaneous water diuresis with recovery had been well established.

The Hepatorenal Syndrome. During the period 1923 to 1943 there appeared a voluminous amount of literature dealing with a group of clinical pictures variously named the "hepatorenal syndrome" or "liver death"[9,10,33-37,53,63,80,81]. These papers presented evidence for a clinical syndrome of hyperpyrexia, shock, jaundice, coma, and oliguria in varied combinations, with death, usually postoperative, of patients suspected for various reasons of having liver disease. Heyd[36], the originator of this concept, after several nosologic revisions, ultimately classified the patients into 3 categories: Group 1 included patients in whom rapid death was associated with hyperpyrexia and coma. The patients were usually obese, had been operated upon for gallbladder disease, did not emerge from anesthesia, and passed rapidly into coma with high fever, dying in a day or two. The patients in Group 2 tended to exhibit obstructive jaundice, with long histories of severe hepatobiliary dysfunction. Four to 7 days postoperatively they became stuporous, oliguria and coma appeared, sometimes with fever, and the terminal picture resembled that of classical hepatic coma of patients with cirrhosis or acute yellow atrophy. In the patients in Group 3, hyperpyrexia was absent, and coma, when it occurred, was a manifestation of the renal failure which heavily dominated the clinical scene. These patients had severe hepatobiliary disease; operative intervention was succeeded by profound shock, following which oliguria, anuria, and progressive azotemia appeared, with death occurring at various intervals after the appearance of renal shutdown.

Considerable literature, based primarily on clinical case studies only rarely correlated with postmortem observations, grew up around this concept, which was held in high regard, mainly in surgical circles. Touroff[78], in a study of the Group 1 syndrome, concluded that most patients placed in this category clinically were probably suffering from overwhelming and unrecognized postoperative infection, and he presented a number of autopsied cases in which, although the diagnosis of liver death with hyperpyrexia could have been made clinically, autopsy revealed the actual cause of death to be undiagnosed infection.

Lichtman and Sohval[46] in an important publication condemned the indiscriminate use of the label "hepatorenal syndrome" whenever evidence of damage to both the liver and kidney appeared, and elaborated a sound and

comprehensive classification of the various unrelated situations in which such observations were noted. They emphasized that surgical procedures were unnecessary to produce renal damage in patients with hepatic disease and expressed the view that it was scientifically unsound to evoke a special hepatorenal syndrome to explain most instances of death following operations involving the biliary tract. In retrospect, it appears that whereas interest in the hepatorenal syndrome served a useful purpose in focusing attention on the tremendous importance of careful pre-operative preparation for patients with liver disease, the concept of a specific hepatorenal syndrome occurring postoperatively will not stand critical scrutiny. Fulminating infections probably accounted for the deaths in Group 1, those in Group 2 mainly represented the more conventional pattern of metabolic liver failure precipitated by operative intervention in patients with extensive pre-existent hepatic disease, and those in Group 3 today would probably be diagnosed as lower nephron syndrome secondary to shock.

The occurrence of degenerative lesions involving the renal tubules in the presence of deep jaundice, or cirrhosis with or without jaundice, has been observed repeatedly[3,5,16,74], and the coexistence of chronic nephritis and hepatic cirrhosis has recently been commented upon[19,55]. A clinical study of renal function in acute hepatitis has shown diminution in concentrative power, decrease of urea clearance, as well as increase in urinary content of protein, casts, and erythrocytes[24], and elevations of nonprotein nitrogen in both parenchymal and mechanical icterus have been correlated with increased case fatality rates[51]. Thus, whereas description of a specific hepatorenal syndrome does not appear justified, ample evidence for simultaneous involvement of the liver and kidney exists, and the mechanism of renal implication in many instances is not apparent.

Antidiuresis. In 1940, Robinson and Farr[65] published an important paper attempting to correlate with a urinary antidiuretic substance the presence of edema in acute hemorrhagic nephritis, sulfonamide nephropathy, the nephrotic syndrome, premenstrual edema, and several other states. Using a slight modification of the rat assay method of Burn, they demonstrated the presence of a substance in the urine of these patients which was definitely antidiuretic to hydrated rats and which disappeared from the urine after the edema had subsided. They studied no patient with hepatic disease.

Five years later, Ralli and associates[62], applying the Burn technique in the testing of the urine of patients with cirrhosis, found that the urine of patients with ascites contained large amounts of a substance which was antidiuretic to rats but which did not stimulate the excretion of chloride. After the formation of ascites had ceased with improvement of the cirrhosis, the same patients, as well as some with cirrhosis who had never had ascites, and dehydrated normal individuals all had much lower but still definitely measurable titers of antidiuretic factors in the urine. The presence of such factors has been amply confirmed[32,45], but their identity remains a subject for further study. It has been suggested that the factor is the antidiuretic principle of the neurohypophysis, but as Smith[72] concludes in his recently published monograph, it seems unlikely that the substance in the urine of patients with cirrhosis is "antidiuretic hormone, its normal excretion product, or pitressin, despite its antidiuretic activity in rats, since it has no antidiuretic activity in dogs." Ralli and Leslie[60] have recently summarized

their views on antidiuretic factors found in the urine of these patients, concluding that the substance has not yet been identified and should be referred to, not as the antidiuretic hormone, but simply as an antidiuretic substance.

Ralli and associates[61] recently reexamined the delayed water diuresis of patients with cirrhosis, corroborating the results of earlier investigators. It was also found that the serum sodium chloride fluctuated more widely in the cirrhotic than in the control subjects and that in the patients with cirrhosis an increase of 3% or more in serum concentration of sodium chloride occurred at the time the minute volume of urine was decreasing. They suggest that this increase might suffice to stimulate the antidiuretic mechanism of the neurohypophysis.

Labby and Hoagland[43] studied intensively and repeatedly alterations of water storage and excretion as well as changes in blood and plasma volume and in extracellular fluid volume in a group of 14 patients with acute hepatitis. Serially they measured the Evans Blue plasma volume and extravascular thiocyanate space, along with urinary excretion of chlorides, plasma chlorides, and water tolerance test, as hepatitis of varying degrees of severity subsided. This important study proved that during the acute phase of the disease there was a significant expansion of plasma and total blood volumes and thiocyanate space, with depression of the serum chloride level and urinary chloride excretion simultaneously with a tendency to retain an ingested test load of water. "With convalescence and improving liver function, shrinkage of the thiocyanate compartment and a decrease in the total blood and plasma volume occurred. A diuresis and decreased tendency to retain ingested water were noted at this time, and a rise in plasma and urinary chloride levels followed." They suggested the possible influence of endocrine factors and also called attention to the urinary excretion of increased amounts of biologically active estrogens, an aspect which will be examined later in more detail.

Farnsworth[22], reporting in 1948 on her observations of sodium and chloride excretion in patients with edema associated with cardiac failure, nephrotic syndrome, and hepatic cirrhosis, observed sodium excretion in the patients with cirrhosis to be remarkably diminished, only traces being noted in some. In this group the urinary "sodium-chloride ratio was even more sharply reduced than in the cardiac group." She concluded that the fluid retention of both clinical states was a result of "disturbances of electrolyte metabolism intimately associated with the renal tubules." In a subsequent communication with Krakusin[23], she demonstrated that in cirrhosis as in congestive heart failure, though renal clearances of mannitol and para-aminohippurate may be somewhat reduced, the metabolic functions of the kidneys are not materially affected, other electrolytes exhibiting the expected variations in response to intake. The same investigators observed only modest sodium and water diuresis following injection of mercurial diuretics. They suggested that the stimulus to water and salt retention was a specific one and that the same stimulus was acting in both cirrhosis and congestive heart failure.

Eisenmenger and co-workers[14] independently made observations on patients with cirrhosis similar to the ones previously cited. In their patients with cirrhosis and ascites there was complete cessation of ascites formation when salt intake was limited to 1.0 gm. daily, and there appeared to be a critical level of 1.2 gm. daily, above which formation of ascites reappeared.

No matter how much salt was ingested, the kidneys excreted between 0.02 and 0.13 gm. daily. Numerous subsequent contributions[12,21,40,48,56] have provided rational palatable high protein–low salt diets which are not too difficult to enforce and which have proved most useful in the clinical management of patients with cirrhosis and ascites. Eisenmenger and co-workers[15] extended electrolyte observations on patients with cirrhosis to include sweat and saliva; their studies confirmed the previously noted sharp decrease in renal excretion of salt and revealed reduced concentrations of sweat sodium and low levels of saliva sodium with increased salivary ratios of potassium to sodium. Lowest levels of serum sodium appeared to be secondary to maximal ascites formation, and rises in serum sodium and increased amounts of urinary sodium were apparent before the grosser changes in water balance were detectable. These investigators advanced the possibility that a generalized humoral effect resembling that of the salt hormone of the adrenal cortex might be responsible for the sodium retention and suggested that such humoral influences were not primary but were essentially protective owing to formation of excessive ascites.

Further to investigate the problem of salt retention in patients with cirrhosis and ascites, and especially to evaluate the "availability" of salt for excretion and the presence of "antisaluretic" and antidiuretic factors, Goodyer and associates[30] investigated renal function and salt excretion after infusion of hypertonic saline solution. They found that normal subjects and patients with cirrhosis but not ascites excreted a much larger amount of the injected sodium than did patients with edema or ascites or with both, though the levels of the serum sodium rose about equally in both groups. Most of the subjects with cirrhosis had normal glomerular filtration rates (mannitol) and renal plasma flows (para-aminohippurate), so the results were interpreted "as evidence of a specific impairment of the renal mechanism for the excretion of administered sodium in cirrhotics with edema and/or ascites", and as suggesting increased tubular resorption under a stimulus thus far unidentified. Sims[70], studying 15 patients with cirrhosis and ascites, observed normal glomerular filtration rates and renal plasma flows in 9 and slightly reduced values in 6. All showed reduced sodium and chloride excretion and all but one exhibited increased amounts of urinary antidiuretic substance, though the latter could not be correlated with the other changes. Similar studies have been published by Epstein and coworkers[19].

Parenthetically, Merrill[50] has shown the sodium concentration in sweat to be lower in patients with congestive heart failure than in normal individuals; others have demonstrated a decrease of sodium and chloride and an increase of potassium in the saliva of patients with congestive failure[79]; and the urine of patients with congestive failure has been found to exhibit increased corticoids[54] and antidiuretic principles[7]. Eisenmenger and associates[15] mentioned in passing a similar observation in patients with cirrhosis. The two states, cirrhosis and congestive heart failure, appear similar indeed in terms of salt excretion, and it is inviting to agree with Farnsworth that the stimulus to salt retention in both states is identical.

Similarities between sodium retention of patients with cirrhosis and the physiologic effect of the salt-active adrenal steroids are obvious, and that certain gonadal steroids have similar salt-retaining effects is also well established. Thorn and Emerson[75], studying the well known phenomenon of pre-

menstrual edema, observed that in normal women cyclic changes in excretion of sex hormones were associated with definite variations in excretion of sodium, chloride, and water. These changes, salt and water retention, did not occur in a patient whose uterus and ovaries had been removed but were noted in a hysterectomized patient with intact ovaries. They observed also that in patients with the ascites of cirrhosis the volume of the ascitic fluid increased during the premenstrual period. Attention was also called to the DCA-like effect not only of estrogen but also of progesterone and testosterone. This study, with others[73,76,77], left no doubt that estrogen, progesterone, and testosterone had sodium-retaining effects closely resembling those of DCA. Because premenstrual retention was more striking than that associated with ovulation, it was proposed that progesterone alone, or progesterone in combination with estrogen, was more effective than the latter alone. Which of these principles or what combination is responsible, or whether they act directly or indirectly upon the renal tubule, cannot definitely be stated at this time.

In any case, the electrolyte disturbances occurring under the influence of salt-active steroids closely resemble those observed in the presence of both acute and chronic liver disease, and evidence for the presence of increased estrogen excretion in young males with acute hepatitis has been presented by Gilder and Hoagland[25], and in cirrhosis by Glass, Edmondson, and Soll[27]. Further liver–gonadal relationships will be discussed later; at this point attention is merely called to the potentialities of salt-active steroids in mediating the electrolyte disturbances described.

Worthy of mention at this point are the extensive experiments of Shorr and associates[4,67-69]. Without a discussion of their researches on the balance between VEM (a renal vasoexciter) and VDM (a hepatic vasodepressor), it perhaps will suffice to point out that VDM concentrates, as well as ferritin and apoferritin, with which VDM has been identified, are capable of producing antidiuresis in hydrated rabbits and dogs. The same investigators found that in all subjects with edema and antidiuresis there were appreciable amounts of VDM in the circulation. They have tentatively concluded that VDM exerts its antidiuretic effect by stimulating the posterior pituitary to discharge antidiuretic hormone. Rats with granulosa cell tumors have been found to have tremendously augmented blood volumes and greater amounts of circulating VDM, and it has been postulated that enlargement of the capillary bed caused by the VDM requires increasing the blood volume—but one could speculate along other lines—that salt retention occurred under the influence of steroids produced by the granulosa cell tumor, that the water excretion was curtailed through the ADH mechanism, and that increases in VDM were associated with adaptation of the capillary bed to the increasing blood volume. The importance of VDM in the guidance of salt and water movements has not yet been conclusively established, though further investigation may identify it as an important link in the chain which produces salt retention.

That the liver plays an important physiologic role in metabolism of hormones in general and of steroid hormones in particular has been demonstrated. A recent review by Glass[26] has assembled most of the pertinent references, and only a few salient features discussed in this communication will be mentioned here. For many years there has been evidence at a clinical level of a relationship between hepatic dysfunction and gonadal hormone ac-

tivity, particularly exemplified by the Sylvestrini–Corda syndrome of testicular atrophy and gynecomastia occurring in the presence of hepatic cirrhosis in men[13]. The familiar cutaneous arterial spider angioma is perhaps causally related to humoral imbalance[6]. Gynecomastia developing during the recovery phase of extreme malnutrition has been thought to be a manifestation of persistent nutritional liver disease, though the curious fact that the gynecomastia occurred not during the period of inanition but during the period of recovery has not been completely explained[38]. It has been suggested that during starvation production of both androgens and estrogens is reduced. Restoration of nutrition allows both to be formed again, but the residually damaged liver is unable to inactivate excess estrogen, leading to an abnormal estrogen/androgen ratio.

Both Glass[26] and Lloyd and Williams[47] have reviewed in considerable detail the main features of hepatic influences on the effects of gonadal hormones. Briefly, there is evidence that the liver inactivates androgens, estrogens[17], and progesterone[18,49] and that the androgens are much more readily disposed of than are the estrogens[8]. Progesterone is only slowly inactivated[18]. Not only is inactivation available as a mechanism, but the probability of biliary excretion and even of enterohepatic circulation has been established[11]. Estrogen–protein complexes have been shown to be present in the blood[64], and the liver may well play an important role in the formation and homeostasis of such complexes. Numerous investigators have demonstrated that inactivation of sex hormones occurred when they were circulated through the liver, and increased estrogen activity has repeatedly been observed following damage or partial removal of this organ[66].

Gilder and Hoagland[25] found increased urinary estrogen activity in young males with hepatitis, and, studying patients with cirrhosis, Glass and associates[27] encountered increased urinary estrogen values, all due to the free or unconjugated steroid, with decreased androgen concentrations. These observations were interpreted as evidence for the fact that reversal of the ratio of androgen to estrogen produces demasculinization and as a clinical example of the difficulty of hepatic inactivation of estrogens as compared to androgens. Without further citations from the abundant literature which has accumulated around this subject, it may be recapitulated that the liver exerts a profound influence on the physiologic activity of the sex hormones, through selective inactivation, excretion, conjugation, and perhaps through interconversion. That similar influences are operative in the cases of other steroids of adrenal origin also seems probable, since experiments of the estrogen inactivation type have been applied to DCA, yielding evidence of *in vivo* inactivation when pellets were implanted intraperitoneally[31]. Indeed, it seems possible that amelioration of the symptoms of rheumatoid arthritis in the course of intercurrent hepatitis might be mediated through enhancement of activity levels of adrenal steroids due to reduction and alteration of hepatic inactivation. Such a mechanism, through hypoxia and reduction of hepatic blood flow, might account for the old clinical observation that with the onset of congestive failure, the florid febrile and arthropathic manifestations of acute rheumatic fever occasionally subside strikingly.

The liver, incidentally, has been shown to inactivate pitressin[20], and the possibility of hepato-equilibratory influences on the trophic hormones of the

adenohypophysis awaits the advent of new and more refined techniques.

The rather striking similarities of the sodium retention in acute and chronic hepatic disease and congestive heart failure suggest that a similar stimulus is present in all. If one wishes to postulate that this stimulus to the renal tubule is a steroid hormone of adrenal, gonadal, or perhaps other origin produced in usual amounts (or even increased quantities, under the stress of disease), rendered physiologically more effective through the mediation of decreased inactivation, then it is perhaps possible to explain water retention through a secondary activation of a water-retaining mechanism of posterior pituitary origin. Kark and associates[41] have recently studied a group of patients with cirrhosis in an attempt to elucidate the possibility that sodium retention in this disease is a manifestation of adrenal mineralocorticoid activity. They found extremely low urinary levels of 17-ketosteroids and definitely elevated urinary cortins. As these investigators suggest, precise evaluation of urinary salt-retaining steroid concentrations awaits refinements in methodology. They offer the suggestion that adrenal dissociation may be present, to explain the apparent reductions in N-hormone in the presence of increased urinary cortins. With acute and chronic liver disease the defect may be primarily hepatic and with congestive heart failure secondarily hepatic through decreased hepatic blood flow, hypoxia, or other mechanisms. Salt retention in such a scheme need not be exclusively a matter of renal tubular enzymes but might also be mediated through alterations in renal blood flow by humoral influences.

Summary. Selected observations on hepatic influences in the homeostasis of extracellular fluids are reviewed. Attention is again called to the role of the liver in the physiologic equilibration of the effects of steroids with both sexual and renal tubular influences. The possibility that increased activity levels of salt-active hormones is the common denominator of water and salt retention in both hepatic disease and congestive heart failure is recalled.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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PSYCHOLOGICAL PROBLEMS IN PHYSICAL REHABILITATION: A REVIEW

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SINCE World War II the medical literature has contained progressively more material on rehabilitation. This is a healthy state of affairs, yet somewhat surprising when we consider our concern in medicine with the spectacular, the brilliant diagnosis, the rapid and gratifying treatment. As an editorial in Lancet put it[9]: "The detective side of medicine—investigation and diagnosis—has such charm that many doctors never get over their early preoccupation with it. . . . Nowadays we talk freely of reablement . . . (which) . . . is long term trouble, and we have agreed to think of long term trouble as dull. To be disabled is a massive experience: the mind suffers with the body, and every disabled patient presents, in current jargon, a psychosomatic problem."

Much of the pioneer work in the rehabilitation field has been done by Howard Rusk[25,27], who has publicized it as the "Third Phase of Medicine." Rusk has always clearly emphasized the importance of the psychological factors in the rehabilitation process. He has called attention to the fact that successful recovery is "not miracle but motivation," and that people with physical disabilities have more frequent and severe adjustment problems than people without injuries and deformities. For many years psychiatrists working with hospitalized neuropsychiatric patients have realized the usefulness of physical agents in therapy[8,32]: tubs, contrast showers, packs, massage, and the like: but the utility of the psychiatric approach to the rehabilitation of the physically disabled is a new concept to most. Rusk[25] has done much to popularize and apply this in actual rehabilitation practice. The psychiatrist, along with the social worker and psychologist, is becoming an integral part of the rehabilitation team in many centers.

Patient's Reaction to Disability. The ways in which a patient's psychological reaction to his disability, to efforts to overcome it, to his doctors, physiotherapists and nurses, can affect his rehabilitation program and progress are important. They are frequently demonstrated in practice, and generally quite understandable. One of the first problems confronting the physician dealing with chronic illness and injury is in the patient's acceptance of the disability. Each of us has a conception, fixed through the years and largely unconscious, of our bodily configuration: our "body image", as Paul Shilder expressed it many years ago. Grayson[13] has commented on the difficulty many injured or ill people

have in accepting any radical changes in their "body image." As he points out, we frequently see people who honestly tell us they have no idea of their disability and its prognosis, despite having seen numerous reputable physicians about it. Unless this inability to accept one's handicap and its implications can be overcome, the rehabilitation process may be seriously interfered with. The patient may resist necessary corrective operations, such as the fitting of braces, and by his denial of disability make realistic vocation planning impossible.

Another type of reaction seen to bodily injury is reported by Rose[24]. Four patients were seen who developed severe depressive reactions following major surgery. He felt these represented an inability to face their loss realistically. One patient apparently initially denied to herself the loss of her leg, and then developed a severe depression several days postoperatively, as she slowly allowed herself to become aware of the loss and its implications.

Saslow[28] mentions some of the reactions to be expected in patients at the time of announcement of a serious and personally traumatic diagnosis. He is referring specifically to the diagnosis of tuberculosis, but the same reactions may be seen whenever the patient is suddenly faced with adverse news concerning his condition. He may: 1) be very apathetic, apparently stunned and unaware of the real implications of the diagnosis; 2) question or contest the diagnosis or decisions; 3) cry with fear; 4) become markedly hostile and blame his difficulties on others; 5) accept it stoically as needed punishment; 6) accept it with a smile, yet demonstrating to us later his essential inability to believe it. Other types of abnormal reactions may be seen. The importance of recognizing them as abnormal and as possible barriers to later successful rehabilitation is emphasized.

Rehabilitation Problems. During the rehabilitation process itself other psychological problems arise. Undoubtedly the most acute conflicts come up over the necessity of becoming dependent on hospital and rehabilitation personnel. As has been noted by Overholser[19], Boyle[4], Nagler[18], and others[35], dependency problems can become very disturbing both to the patient and to the physician or others involved. An overly dependent person makes difficult demands on us, and becomes hostile, upset, and often depressed if these are not met. Because of fears of dependency other patients are unable to form friendly relationships and always remain hostile, on the outside, and largely apart from our help. Some patients, who have never struggled successfully or with any degree of conviction, may use injury and illness as a welcome refuge and regress, if possible, into an apathetic stage of complete dependence. Overholser[19] mentions that erotic satisfactions from manipulations may increase the dependency, and also create awkward situations requiring "tact and discretion." He notes this to be particularly true in patients with marked homosexual trends.

The event of leaving the hospital or rehabilitation service may also produce problems in this same sphere, as is pointed out by Saslow[28]. The threat of loss of support and friendships, coupled with the fears of competition in the outside world, may produce hostilities and set-backs, unless adequately handled. Relapses at this time are not uncommon and the psychological factors behind them should be looked into. Overdoing may represent a reaction to fears over abilities to compete successfully, or, as is occasionally seen in tuberculosis patients, unconscious desires for a breakdown

with resulting return to the safety and comfort of the hospital.

How these reactions can interfere with successful rehabilitation is not difficult to understand. How to deal with them successfully is quite another problem. However, the recognition of their existence and the identification of them when they are operating in the rehabilitation program is in itself a great step forward toward their successful management. Overholser[19] and Saslow[28] have pointed out that the majority of these problems are not for the psychiatrist to handle but are within the province of the physiatrist, the surgeon, the orthopedist, the internist, and those closest to the case. Seidenfeld[30] has emphasized the importance of the physician's allowing the patient to "get it off his chest," of the patient's being able to discuss his fears, worries, and uncertainties. Saslow[28] points out that we should not interfere with the patient's emotional reaction to our decisions, but should discuss them freely with the patient and not shy away from their hostility, even when directed toward ourselves. Long and Roth[15] enumerate such human qualities as sympathy, understanding, and responsiveness to behavioral symptoms as being necessary in a good "rehabilitator." Other sources[35] touch on a common failing we all have as physicians: rejecting the patient who improves only slowly. They note the necessity of finding out the psychological factors behind the failure.

Boyle[4] indicates we can circumvent or decrease some of the psychological problems of rehabilitation by careful planning of the program and of the facilities and environment in which the program is carried out. He feels that continued care in the conventional hospital leads to "mounting dependency and regression." As he puts it, too much of a protected experience leads to loss of ability for independent living, and he calls for a "dynamic" rehabilitation program in special centers apart from the usual hospital surroundings. He feels this will "minimize the infantilization inherent in every institutional program."

Special Problems. Certain special rehabilitation problems exist and carry with them rather special psychological problems. The Veterans Administration[35], in its pamphlet on rehabilitation of neurological cases, notes the occasional cases of conversion, compensation and post-traumatic reactions. They also point up the role of the psychological testing in these situations. At this point we should digress a moment to point out that psychological testing, particularly from the standpoint of personality evaluation, can be of great value to both the psychiatrist and the non-psychiatric specialist assessing difficult rehabilitation problems. The widened applications of the Rorschach and the Thematic Apperception Test (TAT) to the understanding of basic personality structure are of both clinical and research significance. As part of the rehabilitation team, the psychologist can tell us much regarding the patient's emotional stability, motivations, skills, and interests. He can help us assess the patient's assets and liabilities. This is of particular value when the illness or injury has involved the central nervous system. He also may give us useful and concrete information helpful in advising relatives and prospective employers about what to expect in terms, again, of assets and liabilities.

Deformities. To return to these special rehabilitation problems, Seidenfeld[30] points out the discouraging effects of severe deforming disease and injuries on the person afflicted. He notes the necessity of early formulation to the patient of operative and prosthetic programs as well as voca-

tion planning; all this as an aid to "morale". Nagler[18] reports his observations on a large number of paraplegics and notes the psychological aspects of loss of bowel and bladder control and complete or partial loss of sexual function. He mentions their difficulty in facing the reality of their condition and the frequency of false hopes that function will return. This at times is said to lead to their refusal to allow and cooperate with necessary rehabilitation measures. The danger of drug addiction in the more dependent paraplegics is mentioned, and he emphasizes the prevalence of feelings of resentment and inferiority that must be dealt with before rehabilitation can be successful.

Rheumatoid Arthritis. The treatment and rehabilitation of rheumatoid arthritics raises special and interesting problems. From the standpoint of psychosomatic research there are several studies concerning the etiology and course of the disease. Ludwig[16] has attempted to enumerate certain personality characteristics common to this group, and gives us the picture of overactive, overworked, highly sensitive, superficially calm individuals seething inside like a "volcano" with inner strain and tension. He pictures rheumatoid arthritics as people capable of extreme rage which is taken out internally through tremendous discharges into the somatic motor and autonomic systems. Alexander[1] elaborates further on some of the possible mechanisms by which emotional problems may produce or at least contribute to a disease with such marked organic deformities. From his general discussion of etiology, Ludwig[16] suggests certain modifications of our medical and physical treatment of the disease: 1) avoid situations in treatment which will arouse the patient's anger; 2) convince the patient of the rationale of the treatment, 3) give the patient strong emotional support during the acute phases of the illness; 4) help the patient to understand his emotions and to develop ways of externalizing them. Bauer[3] also emphasizes the necessity of considering the role of emotions in the etiology and course of the disease and underscores the effects of the added trauma of the disease on the patient's psychological process. He mentions the necessity of understanding the patient's fears of the disease and of helping him to lessen these. He also mentions the need of helping him to gain insight into the effect of psychogenic factors in the cause of the disease.

Psychogenic Rheumatism. The problem of psychogenic rheumatism is discussed by Tegner *et al.*[34]. They bring up the frequency of severe arthritic complaints for which no physical basis can be found. From the standpoint of differential diagnosis they note the extensive distribution of the pain, the relatively slight disability, the frequent use by these patients of such terms as "shooting," "numbness," "terrible," and "hard to describe" in relation to their symptoms. Also the frequency of associated symptoms of depression, tension, phobias, and others in these patients, as compared with those having demonstrable joint pathology, seems significant. They mention the difficult therapeutic problems that these patients present, and point out their general lack of response to physical measures. "To treat them with passive physiotherapy is to acquiesce in their diagnosis of disease and to allow it to take deeper root." They do not claim too satisfactory results with psychotherapy, but suggest it as the best solution available. From the standpoint of physiotherapy this brings up the point raised by Overholser[19]: the need to recognize the primary psychogenic nature of some of the complaints treated by physical medicine. Particularly is this true

of atypical hysterical paralyses. It emphasizes the need, again, of the psychiatrist working closely in the rehabilitation team.

Back Pain. The problem of low back pain and its frequent psychogenic etiology is ably dealt with by Solomon[33] and Paul[20]. Solomon reports good therapeutic results with psychogenic back pain using what he calls analytically oriented psychotherapy along with prescribed recreation and exercise "designed to help release aggression." Paul[20] warns against the use of "passive physiotherapy" in cases diagnosed as psychogenic back disorders.

Children. The problem of rehabilitation of organically impaired children is interestingly dealt with by Schwartz and co-workers[29] who describe their experience with spastics. They point out the necessity of giving the severely handicapped child tasks that he can handle successfully so that he can learn by a "sum of successfully completed tasks." They simplified the environment primarily by a number of ingenious mechanical devices to improve mobility. They point out that success through the use of such devices leads to increased motivation and further success at more complicated tasks.

Powers[21] and others noted the importance of a good mother–child relationship in the rehabilitation of the physically disabled child. The "concealed disappointment" of the mother, when a disturbed mother–child relationship has existed, is often revealed after a severe injury or illness and can be seen by all, but most particularly the child. The trauma of this to an already injured child may be overwhelming.

Seidenfeld[31] reports on the psychological problems encountered in poliomyelitis in children. He notes in particular the child's anxieties, which stem from what he has heard about the disease and his concepts of it, as well as from the isolation and the new environment of the hospital. He also points out that the parents' fears and guilts may further augment anxieties in the child. The role that can be played by the physician in decreasing the anxieties in the child is very important. Seldom is the direct aid of the psychiatrist needed.

Old People. The problem of rehabilitation of oldsters is one of the major fields of geriatric medicine, a subject recently reviewed in this publication by Frank[10]. Pussey and Simcoe[22] bring up an often overlooked point that can be applied to rehabilitation problems in general: Success in old age tends to be founded on and develop from wise living and good adjustment before old age develops. And, as applied to the general field of rehabilitation: Success in overcoming handicaps often depends on a good basic adjustment prior to illness or injury. Rusk[26] has pointed out the magnitude of the rehabilitation problem in old people and outlined some of the psychological factors to help them lead "a useful, dignified and self-respecting life." Ginzberg[11] has gone into some of the more simple and practical methods of handling psychological problems in geriatrics. The ease with which old people are offended and the need to be friendly and supporting, and to give them the feeling you are on their side is emphasized.

Effect of Emotions. From the standpoint of research in psychiatry, studies on the possible effects of emotions on the skeletal musculature have been interesting. Wolff[37] has reviewed much of this work. He points out that enormously increased electromyographic (EMG) potentials have been recorded from the temporal and masseter muscles in anxious people who have been chronically "gritting their teeth" and

"carrying on." He also notes that there are increased electromyographic potentials from the head and neck muscles in people with headaches, during periods of tension associated with these headaches. Malmo and Shagass[17] used experimental stress conditions and found increased muscle potentials in patients with chronic head and neck conditions. Davis and Malmo[7] correlated muscle tension and emotion stress with an ingenious synchronization of sound recorder and electromyograph. They showed the degree to which emotional stress, as brought out in interview situations can produce increases in muscular tension. The possible application of these observations to rheumatoid arthritis was suggested by Gottschalk *et al.*[12], who showed increased somatic muscle potentials under stressful interview situations in untreated rheumatoid arthritics when compared with control subjects and rheumatoid arthritics under psychoanalytical treatment. Wolff[37] suspects that this increased tone may be analogous to the muscle spasm which occurs about a fractured bone or over a ruptured viscus: a defense reaction meant to be a short-term response to stress but misapplied as a long-term reaction. The final result may be permanent joint and muscle changes.

Group Therapy. One of the most promising developments in psychiatric therapy in this field has been the application of group therapy to rehabilitation problems. Randall and Rogers[23] applied this to the rehabilitation problems of epileptics. Canty[5] found a rather directive form of group therapy helpful in amputee rehabilitation, and Tegner[34] mentions its utility in psychogenic rheumatism. From the standpoint of conservation of time and energy of psychiatric personnel, it has much to recommend it. At times it appears to be useful in patients unapproachable through individual therapy.

The problems of rehabilitation in a military setting and rehabilitation of disabled veterans have been dealt with from the psychological standpoint by Cohen[6] and Wexler[36]. The latter points out the necessity of having medical officers who have an interest and knowledge of emotional factors in charge of rehabilitation, and he reports, with some feeling, the results when this is not the case.

Relatively little literature has appeared regarding just how the psychiatrist can apply his efforts on the rehabilitation team. Hurst, Coleman, and Hornbein[14] have pointed out that from the standpoint of the patients the attitudes and prejudices of the hospital staff are of prime importance, and suggest that most psychiatric problems can be handled by an "enlightened staff." They further point out that the patient is most able to confide in the physician directly in charge of the medical management of the case, rather than in the psychiatrist. They also emphasize the role of the social worker in helping the patient with his emotional problems. They feel that the psychiatrist can best work through informal conferences and counseling sessions with the ward physician, social worker, nurse, and other personnel.

Obviously, certain patients will require the specialized attention of the psychiatrist directly, but the majority of emotional problems can be handled adequately by properly trained and supervised non-psychiatric personnel. Undoubtedly this type of "staff-centered" psychiatric service[14] can do much prophylatically to prevent the development of emotional blocks to the rehabilitation process. The value of this orientation in the training of non-psychiatric personnel is well established. The necessity of psychiat-

ric training for such people is underlined from the physiotherapist's point of view in an article by Smith[32]. Duke University School of Medicine[2] has recently announced a 6-month graduate course in the "Psychosomatic Aspects of Physical Therapy" for physical therapists. This course aims to "develop a knowledge of how to reinforce the effects of the physical procedure with a proper appreciation of the emotional factors." Certainly this itself represents an appreciation of the practical applications of psychiatric principles to physical therapy and rehabilitation.

Much basic research needs to be done to increase our knowledge of psychological principles and the psychiatric applications of these to the rehabilitation process. The last few years have pointed out, however, the utility of the combined physical and psychological approach.

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BOOK REVIEWS AND NOTICES

ADVANCES IN PROTEIN CHEMISTRY. Vol. 6, with Cumulative Subject Index for Vols. 1-5. Edited by M. L. ANSON, Thomas J. Lipton, Inc., Hoboken, N. J.; JOHN T. EDSALL, Harvard Univ.; and KENNETH BAILEY, Univ. of Cambridge. Pp. 549. New York: Academic Press, 1951. Price, $9.50.

THE editors of this well known series hope eventually to provide something approaching a comprehensive picture of the present status of protein chemistry. Subjects covered in vol. 6 include: The Electron Microscopy of Macromolecules, R. W. G. Wyckhoff; Light Scattering in Protein Solutions, P. Doty, J. T. Edsall; Poly-α-Amino Acids, E. Katchalski; Egg Proteins, H. L. Fevold; Natural and Artificial Iodoproteins, J. Roche, R. Michel; Glutamic Acid and Cerebral Function, H. Waelsch; Cross Linkages in Protein Chemistry, J. Bjorksten; The Relation of Protein Metabolism to Disease, H. Pollack, S. L. Halpern.

R. H.

PAUL EHRLICH. By MARTHA MARQUARDT, with an Introduction by SIR HENRY DALE. Pp. 235; 52 ills. New York: Henry Schuman, 1951. Price, $3.50.

THE author, who was Ehrlich's devoted personal secretary from 1902 till his death in 1915, had earlier (1924) recorded her recollections of this extraordinary character (*Paul Ehrlich als Mensch und Arbeiter—Erinnerungen aus 13 Jahren Seines Lebens*). She now offers in English an expanded picture, the more valuable as the earlier work was almost entirely destroyed during the Nazi régime. And yet it is still not a full length biography—doubtless was not intended to be one—but rather a roughly chronological series of pictures of his scientific and personal life. Thus a full consideration of the scientific work of this Nobel prize winner, who in chemotherapy established a new principle of medical treatment and whose side-chain theory is still a pillar of theories of immunity production, still remains to be written. In passing, though Ehrlich's early work on stains is included, one fails to find in either this or the earlier work its application to the classification of blood cell types—a milestone of considerable importance in the development of this new field of hematology.

The author, who was brought to England from Paris in 1946 by Sir Almroth Wright, is now busied with the collection of Ehrlich's papers, looking toward a definitive edition to be published by the Royal Society.

E. K.

MODERN TRENDS IN NEUROLOGY. Edited by ANTHONY FEILING, B.A., M.D., F.A.C.P., Senior Physician, Neurol. Dept., St. George's Hosp. and Maida Vale Hosp. for Nervous Diseases; Consulting Physician, Royal Natl. Orthopaedic Hosp., London. Pp. 717; 202 ills. New York: Paul B. Hoeber, Inc., 1951. Price, $13.50.

MODERN TRENDS IN NEUROLOGY is, according to the preface, designed to aid the busy practitioner in keeping abreast of all of the latest developments in medical literature. This has been accomplished. The book is well and amply illustrated. The various subheadings are easily followed, making it possible for one to look up very readily any aspect of a subject. The book is rather large, but the vast amount of material covered, of course, requires this. To the neurological specialist, this material should not be new. To all others on the fringes, in psychiatry, neurosurgery, internal medicine, and other fields, it should serve as a very excellent reference. Very unusually and appropriately, there is an excellent chapter on Neurological Radiology. It is interesting that while most of the authors are English, their viewpoints coincide with those in this country. All in all, as the editor suggests, neurologists at least should "find this book a valuable and even an indispensable addition to their library."

S. G.

WILLIAM SHIPPEN, JR., PIONEER IN AMERICAN MEDICAL EDUCATION. A Biographical Essay. By BETSY COPPING CORNER. Vol. 28 of the Memoirs of The American Philosophical Society. Pp. 161; 9 ills. Phila.: American Philosophical Society, 1951. Price, $2.75.

THE subject of this biographical essay is well known as a pioneer not only in American medical education but also in the obstetrics of the flourishing young colonies. Sent by his father, of the same name and a leading Philadelphia physician, to study medicine abroad, during most of his year in London he kept a

diary which is presented here *in toto*, together with a translation of his "*De Placentae cum Utero Nexu*" (Edinburgh doctoral thesis, 1761). The diary, which was discovered some years ago by Dr. Hall Pleasants on the floor of an attic among other books and is here published for the first time, gives a good picture of the social life of London in the 1750's, as well as the daily routine of the medical student of those days, with illuminating side lights on its writer's personality.

Surprisingly little is to be found of other writings by this distinguished physician; so that Mrs. Corner's carefully prepared and well written, copiously annotated study is welcome, not only as an entertaining essay but also as a distinct contribution to the knowledge of early American medical life and education. One cannot but regret that Mrs. Corner has preferred in her wisdom not to express her opinion on the Shippen-Morgan controversies about their respective roles in founding our first medical school, and in the disputed administration of the medical department during the Revolution.

The book, printed by J. H. Furst Co. of Baltimore, is pleasing throughout in paper, typography and binding, with interesting and instructive end-papers from a contemporary map of Southwark and the south bank of the Thames in the vicinity of old St. Thomas' Hospital. The book is a credit to both author and the Society that sponsored it. E. K.

THE QUANTITATION OF MIXTURES OF HEMOGLOBIN DERIVATIVES BY PHOTOELECTRIC SPECTROPHOTOMETRY. By FRANCIS T. HUNTER, M.D., Assoc. in Med., Harvard Med. Sch.; Assoc. Phys. and Clin. Pathol., Mass. Gen. Hosp. Pp. 226; 55 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $8.50.

THE author has prepared an excellent handbook setting forth the principles underlying the application of photoelectric spectrophotometry to the quantitation of certain hemoglobin derivatives. Part I is comprised of chapters dealing with technique, mathematical theory, the fundamental geometry of conversion charts and nomograms, and a discussion concerning the choice of nomograms, wave lengths, and dilutions. Part II consists of detailed spectrophotometric procedures for the quantitative determination of oxyhemoglobin, hemochromogen, carbon monoxide saturation, oxygen saturation, neutral methemoglobin, serum pigments, and erythrocyte volume.

In addition to the usefulness of this book for the specific determinations it contains, the laboratory worker will find it helpful in the development of procedures and for the construction of nomograms to suit his own needs. C. Z.

DECOMPRESSION SICKNESS. NATIONAL RESEARCH COUNCIL, COMMITTEE ON AVIATION MEDICINE. Edited by JOHN F. FULTON, Yale University, School of Medicine. Pp. 437; 88 ills. Philadelphia: W. B. Saunders Co., 1951. Price, $8.50.

THIS book is by a distinguished chairman supported by an outstanding group of contributors, all of whom are qualified in their respective fields. Résumés at the end of many chapters increase the ease with which the book may be used. The data are well presented and the bibliography is extensive and modern. Opposite conclusions as to the etiology of decompression sickness are well presented. This book will be useful not only to those associated with flying personnel but also to medical students, teachers, and biologists in general. M. O.

CLINICAL UROGRAPHY: AN ATLAS AND TEXTBOOK OF ROENTGENOLOGIC DIAGNOSIS. By WILLIAM F. BRAASCH, M.D., Emeritus Prof., Urol., Mayo Clinic, and JOHN L. EMMETT, M.D., Assoc. Prof., Urol., Mayo Clinic. Pp. 736; 1769 ills. Philadelphia: W. B. Saunders Co., 1951. Price, $25.00.

THIS comprehensive atlas of the roentgenologic study of disease of the genitourinary system will be welcomed by both urologists and roentgenologists. The large number of roentgenograms have been carefully selected and well reproduced. The section devoted to the normal urogram should aid in avoiding many pitfalls in interpretation. The text has been written with great care and is a precise explanation of the material presented in the illustrations. A section on special urographic techniques is included which contains the method, the indications for, and the interpretation of translumbar aortograms. This book should gain wide acceptance as a reference work for anyone concerned with urographic diagnosis. K. C.

HEART DISEASE: ITS DIAGNOSIS AND TREATMENT. By EMANUEL GOLDBERGER, B.S., M.D., Ass. Attend. Phys., Montefiore Hosp., New York; Cardiologist and Attend. Phys., Lincoln Hosp., New York; Lecturer in Med., Columbia Univ. Pp. 392; 221 ills. Philadelphia: Lea & Febiger, 1951. Price, $10.00.

THIS book covers the entire subject of clinical cardiology in 5 sections: 1) the normal

heart, 2) the abnormal heart, 3) cardiac syndromes, 4) systematic descriptions of cardiac abnormalities, and 5) special conditions complicating heart disease.

Some of the abbreviated discussions and peculiar English give the reviewer the impression that portions of the book were written hastily or represent mere notes. There is also at times an exasperating vagueness, such as "I occasionally prescribe," and there are inconsistencies, such as, "The patient may be out of bed in three weeks. I ambulate my patients in two weeks." The personal pronoun "I" is used frequently but is rarely supported by evidence.

On the whole, the modern viewpoint is presented in a conventional and adequate manner. There is, however, nothing in the subject matter or in the method of presentation which makes this book superior to those already available. L. S.

NEW BOOKS

Facts About the Menopause. By MAXINE DAVIS. Pp. 172. New York: McGraw-Hill, 1951. Price, $2.50.

THIS book is a commonsense, understandable discussion of physiologic and pathologic changes associated with the climacterium. The material is accurately and unemotionally presented and includes in the first 75 pages sections on anatomy and endocrine, physical, and emotional alterations. The last half is devoted to a discussion of hygienic principles applicable to this period of life.

The book may be recommended to any patient approaching the climacterium and will undoubtedly answer most of her questions. J. W.

Your Sinus Troubles and Treatments. By FRIEDRICH S. BRODNITZ, M.D., Pp. 243; 10 ill. New York: Abelard Press, 1950. Price, $2.50.

THE title page gives the purpose of the book: "an authoritative explanation for the layman, with recommendations for the treatment of your sinus conditions, colds, hay fever and other allergies." A specially qualified layman may obtain a comprehensive idea of practical rhinology. The information is correct and the book is written in an enjoyable, popular style. The average reader, however, cannot gain worthwhile knowledge from a few pages on anatomy, physiology, differential diagnosis, medical and surgical procedures. M. S.

Frontal Lobotomy and Affective Behavior. By JOHN F. FULTON, M.D., Sterling Prof. of Physiol., Yale Univ. Pp. 159; 20 ills. New York: W. W. Norton & Co., 1951. Price, $3.00.

THE Thomas William Salmon Memorial Lecture Series receives a valuable contribution in the form of Dr. Fulton's up-to-date review and discussion of available literature on the fronto-temporal complex. The author does an admirable task in presenting a technical and complex subject in an easily read and interesting fashion which should appeal to the clinician as well as the student of research. C. U.

The Microkaryocytes, the Fourth Corpuscles and their Functions. By K. G. KHOROZIAN, A.B., M.S., M.D., Pineville, West Virginia. Pp. 969, over 250 ills. Boston: Meador Publish. Co., 1951. Price, $12.00.

THIS is a report of detailed microscopic studies of all types of normal and abnormal tissues with special fixatives and stains. The extraordinary conclusions are not justified by the evidence presented. The concept that all types of cells, and even blood plasma and glandular secretions, are composed of smaller cells, the microkaryocytes, which arise in yellow bone marrow, seems preposterous. However, the large number of photomicrographs will interest cytologists. G. F.

NEW EDITIONS

Pharmacologic Principles of Medical Practice. By J. C. KRANTZ, JR., Prof. Pharmacol., Univ. of Maryland, and Sec'y Comm. Rev. U. S. Pharmacopeia, 1940-50, and C. J. CARR, Assoc. Prof. of Pharmacol., Univ. of Maryland. 2nd ed. Pp. 1116; 95 ills. Baltimore: Williams & Wilkins, 1951. Price, $10.00.

THE second edition of this well organized and readable textbook has appeared only 2 years after the first. It has undergone extensive revision with many additions, such as new chapters on drugs in the treatment of tuberculosis, rickettsial diseases, motion sickness and the arthridites. One finds things such as ion exchange resins, terramycin, banthine, syncurine, tibione, and others, not just mentioned, but discussed.

As in the first edition, the authors use a historical approach, which should deter students from getting the idea that textbook material is the product of spontaneous generation in the infallible brain of the author.

In the opinion of the reviewer, it is probably the best pharmacology textbook available at this time and certainly the most modern. J. B.

Atlas of Cross Section Anatomy of the Brain (Fifth Section.) By EMIL VILLIGER, Revised by EUGEN LUDWIG, Prof. of Anat., Univ. of Basel. Further Revised by A. T. RASMUSSEN, Prof. of Anat., Univ. of Minnesota. Pp. 78; 63 plates. Phila.: Blakiston Co., 1951. Price, $5.00.

To the reviewer, the appearance of this revision of the Villiger-Ludwig collection of brain sections is very welcome. As the preface states, most books on neuro-anatomy contain some of these sections but none are as complete as this. None answers the purpose that this does. This small book is a must for all who would attempt to master any aspect of the nervous system.

The repetition of the diagrams showing the location of the section opposite each section is praiseworthy. It, of course, obviates the necessity of turning back constantly. The additional para-

sagittal series through the right cerebral hemisphere, which has been added by Doctor Rasmussen, is very helpful and is not found in most texts. In fact, this addition conforms to the high level of performance which the reviewer has been led to expect from Doctor Rasmussen ever since he had the privilege of reviewing neuro-anatomy with him in 1932.

Just one objection to the book comes to mind: This is concerned with the type of binding. It is loose-leafed, although the leaves are not detachable, and while that is advantageous when one wants to turn the page back up, or, perhaps to prop the book in front of one, it would seem to the reviewer that it would lend itself to less permanence. S. G.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100.

ERRATUM

The Editors regret exceedingly that the name of Dr. A. Ashley Rousuck, Clinical Instructor in Medicine, Medical School, Western Reserve University, Cleveland, Ohio, was inadvertently omitted from the title page of the article appearing on page 686 of the December, 1951, issue of the Journal and entitled, "Effects of the Intravenous Administration of Gelatin Solution (10 Per Cent). A Laboratory Study on 24 Patients with Chronic Diseases." Dr. Rousuck was one of the 3 authors of this article.